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AMBULATORY pH MONITORING IN THE MANAGEMENT OF REFLUX

RIGID BRONCHOSCOPY BALLOON CATHETER DILATION FOR BRONCHIAL STENOSIS IN INFANTS

AURICULAR CARTILAGE GRAFTS IN LARYNGOTRACHEAL RECONSTRUCTION

ART AND SCIENCE OF LARYNGEAL PHOTOGRAPHY

COMPARISON OF FUNCTIONAL ENDOSCOPIC SINUS SURGERY UNDER LOCAL AND GENERAL ANESTHESIA

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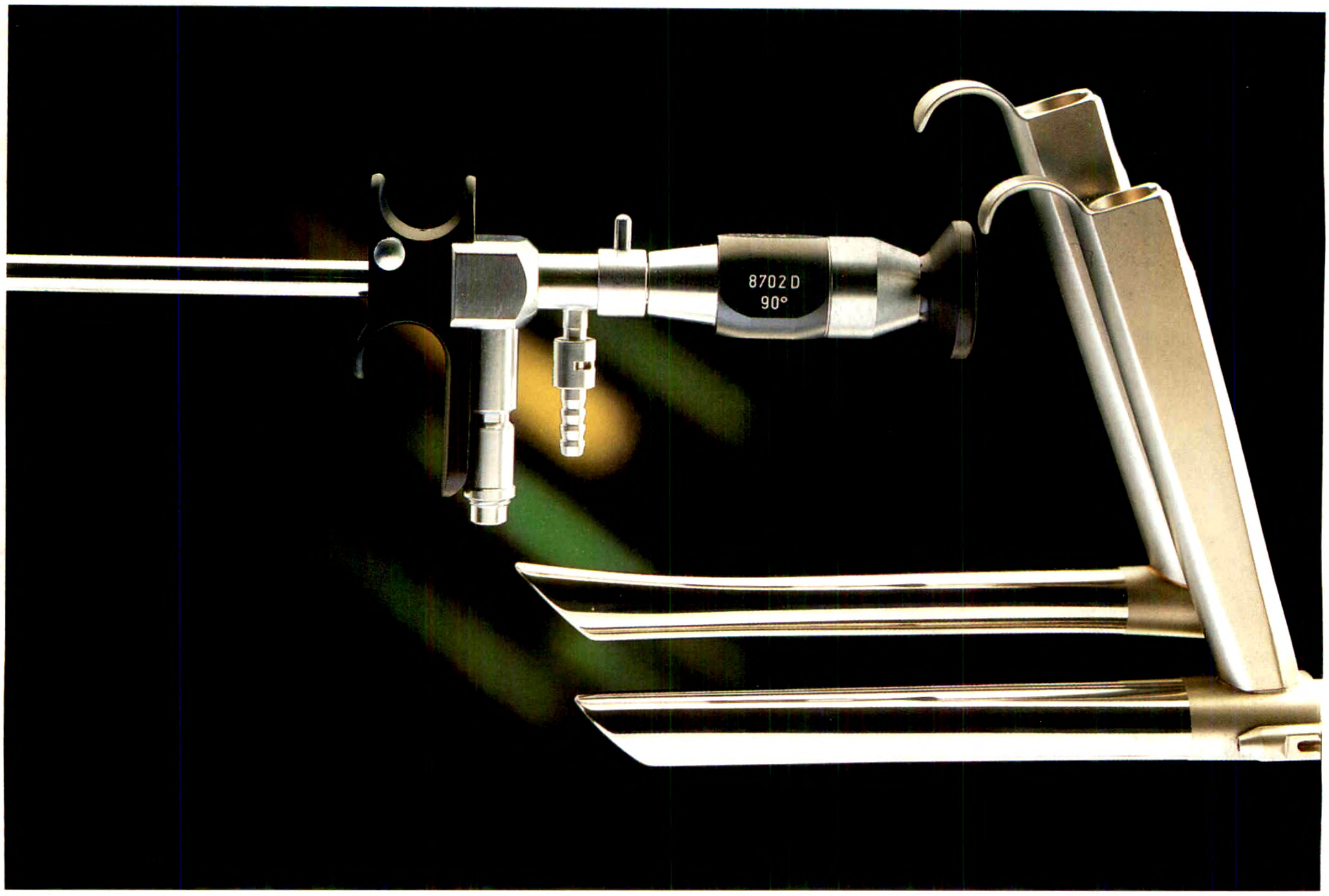

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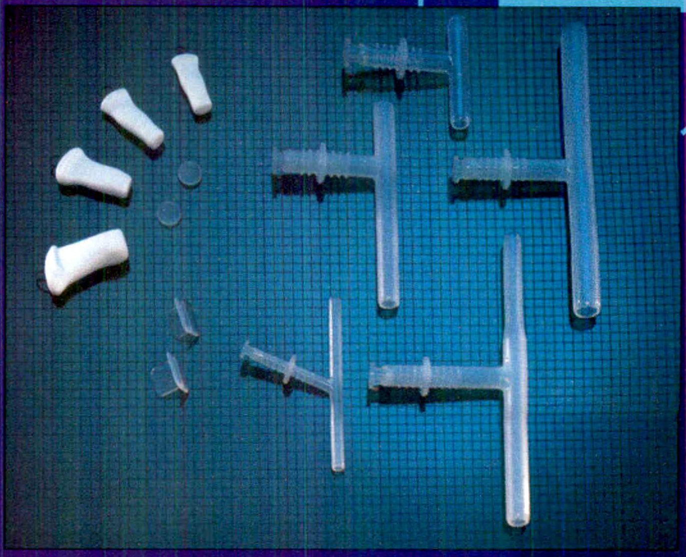

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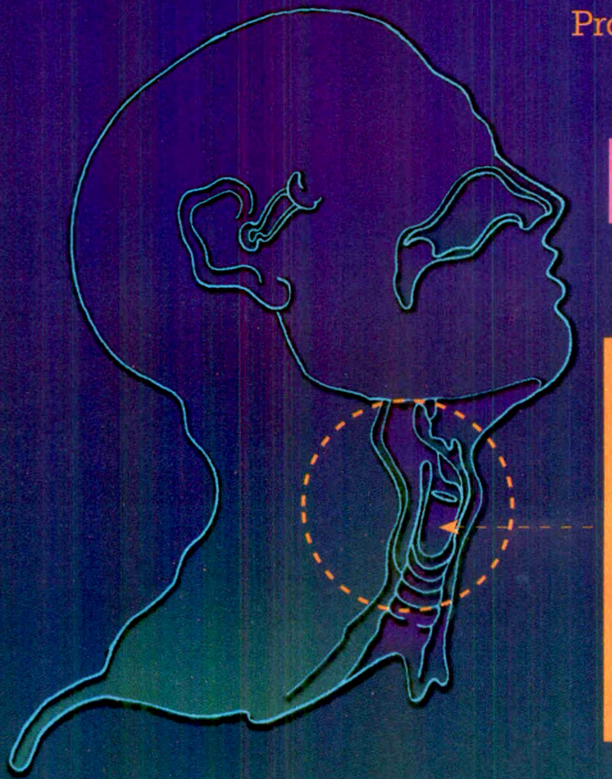

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AMBULATORY pH MONITORING IN THE MANAGEMENT OF REFLUX

MICHAEL FRANK, MD ARNOLD KOMISAR, MD, DDS

NEW YORK, NEW YORK

Ambulatory pH monitoring is a useful tool in the diagnosis and treatment of different esophageal and pharyngeal complaints. We have studied its use in an office setting in 15 patients with suspected gastroesophageal reflux disease (GERD). The patients were monitored for at least 18 hours while wearing a two-channel probe at home. Data obtained confirmed severe GERD in 6 patients and chest pain without GERD in 2 patients. Two patients continued to have symptoms in spite of appropriate therapy, while 2 untreated patients had symptoms of GERD with normal pH studies. We feel this technique is relatively safe and cost-effective and causes minimal disruption of the patient's life-style, while enabling the physician to monitor therapy and help achieve a good therapeutic outcome.

KEY WORDS — ambulatory pH monitoring, gastroesophageal reflux disease, GERD.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a very common disorder of the upper gastrointestinal tract. The cause of GERD may be incompetence of the lower esophageal sphincter, disturbed esophageal clearance capacity, delayed gastric emptying, abnormal esophageal mucosal resistance, or increased irritative capacity of the refluxate.[1]

Patients commonly present with classic pyrosis; however, patients may also have nongastrointestinal symptoms suggestive of a primary disorder of the head and neck. These include hoarseness, foreign body sensation, dysphagia, chronic throat-clearing, and otalgia. A diagnostic dilemma may ensue from attribution of these symptoms to the sinonasal tract. However, paltry physical findings and minimal radiographic changes in the paranasal sinuses should lead one to entertain a diagnosis of GERD.

The diagnosis of GERD has been traditionally made by obtaining the patient's history of reflux. Confirmatory tests have included esophageal manometry, provocative tests with infusion of hydrochloric acid (the Bernstein test), flexible endoscopy, contrast radiography, esophageal scintigraphy, and prolonged pH monitoring. All these tests have their limitations. Difficulties arise in differentiating pathologic from physiologic reflux and correlating reflux episodes with the patient's symptoms. The measurement of esophageal pH changes over 24 hours is one of the most sensitive and cost-effective tests for assessing reflux.[2] Twenty-four–hour pH monitoring in an ambulatory setting enables the physician to correlate reflux episodes with symptoms, even as the patient engages in his or her daily and nocturnal routines.

The use of an esophageal electrode to measure pH was first described by Tuttle and Grossman[3] in 1958. The tests were performed on hospitalized patients over a 24-hour period. These authors concluded that a pH of less than 4 correlated with a diagnosis of reflux. In order to duplicate pathologic reflux in an ambulatory patient, maneuvers such as lateral positioning and the Valsalva maneuver were performed.[4] DeMeester and Johnson[5] and Miller et al[6] reported preliminary results using telemetry for ambulatory pH monitoring. With the development of computer software and miniaturization, portable telemetry was appropriately applied to pH monitoring. This obviated the need for hospitalization and evaluated gastroesophageal reflux under a more physiologic state. Parameters that could be studied in an ambulatory setting included the number of reflux events in both the proximal and distal parts of the esophagus, changes in pH in the supine or upright position, length of reflux events, and activity during or prior to the reflux event. Further refinements in testing hardware included the ability to document pain and mealtimes at the time of pH monitoring.

MATERIAL AND METHODS

Seventeen patients with symptoms suggestive of a diagnosis of GERD were studied over the 2-year period 1989 to 1991 (see Table). Ambulatory pH monitoring was performed on an outpatient basis in 16 patients and on an inpatient basis in 1 patient. One patient had to be studied on two occasions because of equipment failure, and 2 patients could not tolerate the pH probe. The equipment used was a Synectics antimony pH probe with proximal and distal channels (two-channel probe). The distal channel mea-

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From the Department of Gastroenterology, Albert Einstein College of Medicine, Bronx (Frank), and the Departments of Gastroenterology (Frank) and Otolaryngology (Komisar), Lenox Hill Hospital, Cornell University Medical College, New York, New York.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Desert, California, April 13-14, 1992.

REPRINTS — Arnold Komisar, MD, DDS, 1317 Third Ave, New York, NY 10021.

PATIENTS' SYMPTOMS AND PREOPERATIVE STUDIES

Pt	*Age (y)*	*Symptoms*	*Studies and Findings*
1	49	Throat pain	Cine, EGD: hiatal hernia
2	42	Throat pain	Cine, EGD: esophagitis
3	35	Chest pain	EGD: esophagitis
4	57	Chest pain	Cine, EGD: esophagitis
5	60	Chest pain	Cine, EGD: hiatal hernia
6	42	Foreign body sensation	EGD: negative
7	50	Asthma	Cine, EGD: negative
8	31	Heartburn	EGD: negative
9	57	Throat pain	Cine: hiatal hernia; EGD: negative
10	30	Heartburn	EGD: negative
11	64	Heartburn	Cine: hiatal hernia
12	24	Foreign body sensation	EGD, cine: negative
13	45	Chest pain	EGD: negative
14	70	Chest pain	EGD, cine: negative
15	42	Heartburn	EGD: negative

Cine — cine-esophagram, EGD — esophagogastroduodenoscopy.

sured pH just proximal to the lower esophageal sphincter, and the proximal channel measured pH just distal to the cricopharyngeus. Position of the pH probe was determined by measuring the esophagogastric junction endoscopically and confirmed by measuring pH during placement of the probe. Patients wore the equipment at home after placement of the pH probe in the late afternoon in the office. They were encouraged to eat their regular meals without restrictions and to partake of their normal daily and nocturnal routines. Mealtimes, activity, and pain, as well as the pH record, were recorded on a portable transponder. These data were later downloaded in the office to a standard IBM-compatible portable computer using Synectics "eso-ph-ogram" software (Fig 1). Parameters studied included reflux events ($pH < 4$) in a supine and upright position (distal and proximal), total reflux events in a 24-hour period, and length of time of reflux events. If the patients wore the probe for less then 24 hours (18 hours), data were extrapolated for the remainder of the 24 hours. Findings were correlated with patients' complaints, diagnoses, and previous test results.

RESULTS

Fifteen patients were studied with minimal complications. They were able to tolerate the probe without significant disruption in their meals or activities of normal life, although no patient wore the probe to work. Two patients were unable to tolerate the probe, and their studies were never completed. The data were compared to normative data for ambulatory pH monitoring compiled by previous authors. For the percentage of reflux episodes in the monitored period, extrapolated to 24 hours, abnormal values were as follows: for upright position, over 5.85%; for supine position, over 1.81%; and for total time monitored, over 4.39%. These values were those previously reported by Koufman.[7] Values for total number of reflux events and number of events greater than 5 minutes were compared to normative data established by Johnson and DeMeester.[8] More than 35

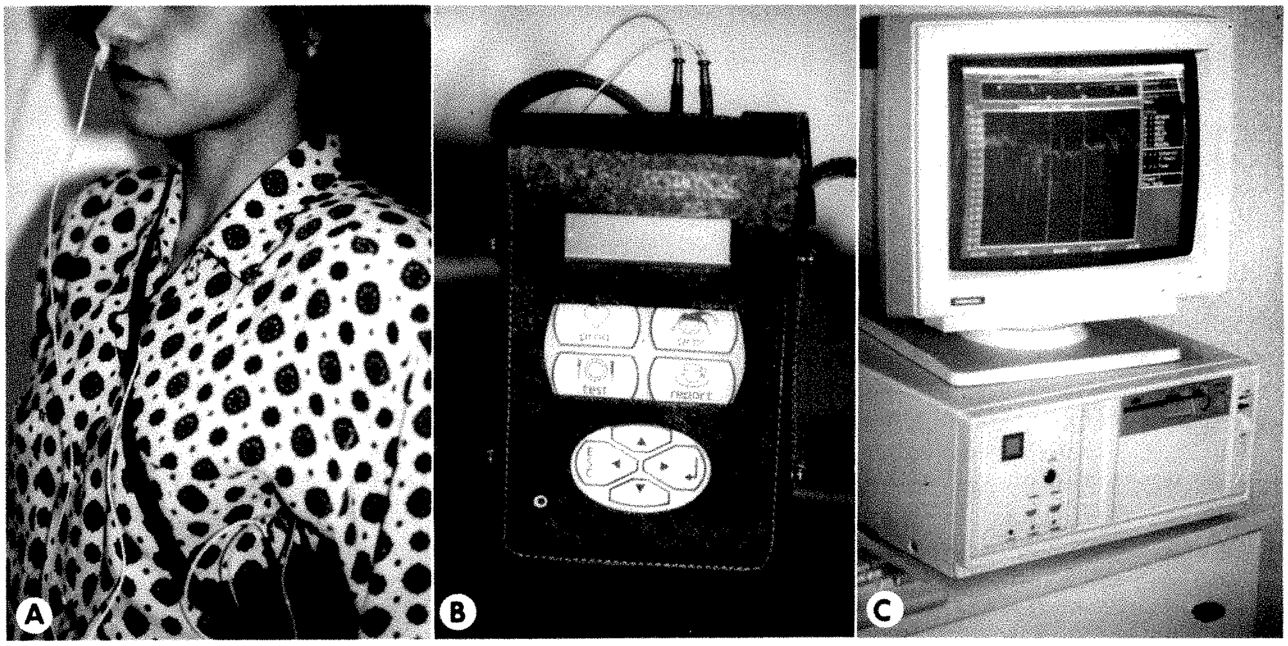

Fig 1. Equipment. A) Patient wearing probe and transponder unit. B) Transponder unit. C) Personal computer running "eso-ph-ogram" software.

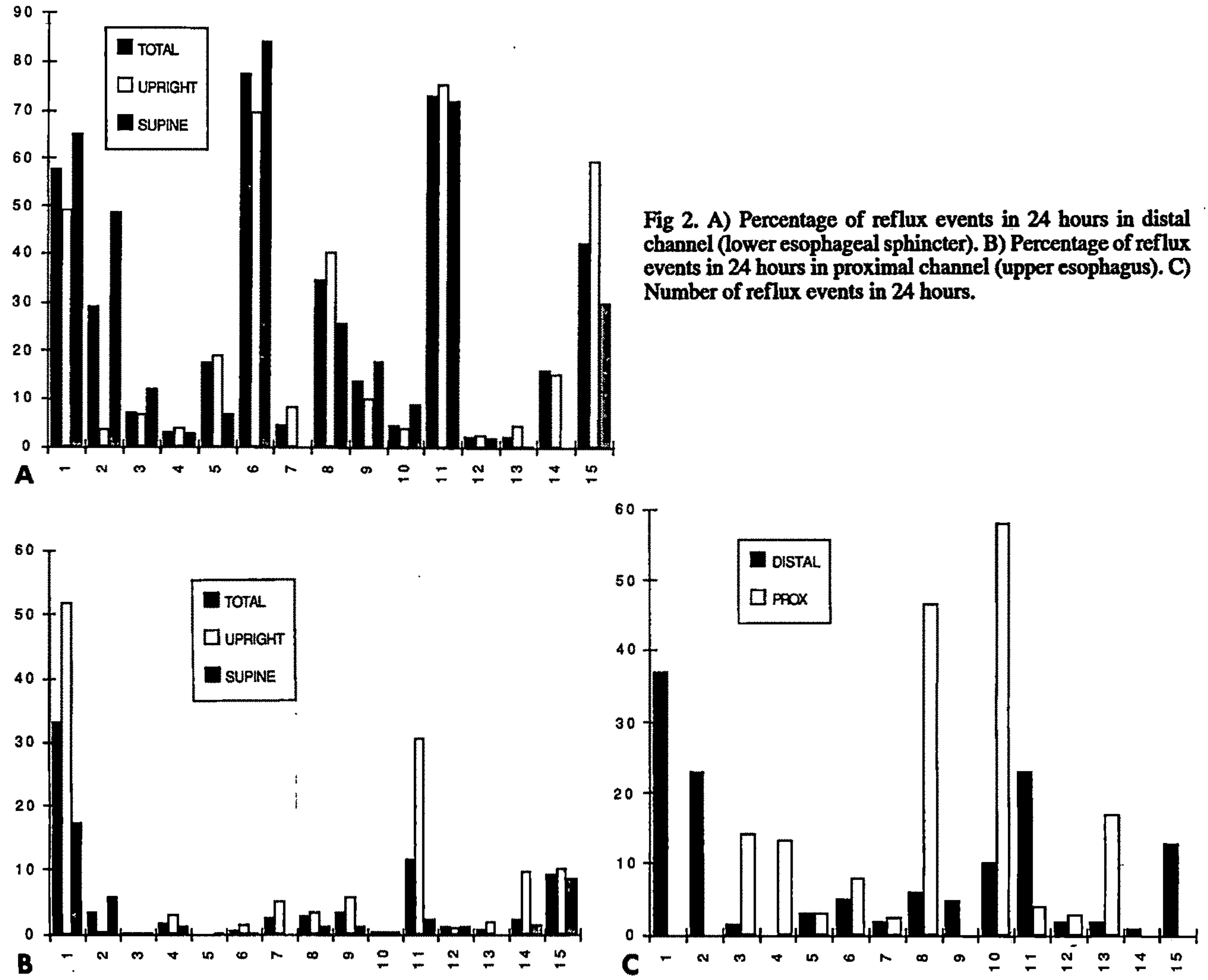

Fig 2. A) Percentage of reflux events in 24 hours in distal channel (lower esophageal sphincter). B) Percentage of reflux events in 24 hours in proximal channel (upper esophagus). C) Number of reflux events in 24 hours.

reflux events in 24 hours was considered abnormal, and more than 5 reflux events longer than 1.8 minutes was considered abnormal. Ten patients had abnormal results for the lower esophageal sphincter in the upright and supine positions. Ten patients had abnormal results when one considered total time monitored at the lower esophageal sphincter. When the upper channel was studied, 6 patients had abnormal values in the upright position and 4 patients had abnormal values in the supine position. Three patients monitored at the upper channel had abnormal 24-hour study results. One patient had more than 35 reflux events in a 24-hour period at the distal channel (lower), and 2 patients had more than 35 events at the proximal channel. Four patients had reflux events greater than 1.8 minutes in length (Fig 2).

DISCUSSION

Ambulatory pH monitoring may be the most physiologically correct test available to confirm reflux. Castell[9] has stated that pH monitoring is the method of choice to evaluate patients with equivocal or atypical symptoms of GERD, chest pain, hoarseness, or asthma. These are patients in whom conventional testing often fails to establish a diagnosis.

While normative data used were based on 24 hours, we often extrapolated data based on 18 hours of monitoring. This was because of the need to enable patients to return to work after 1 day of monitoring. Dobhan and Castell[10] have recently shown that this period of monitoring can be used with equal accuracy. In our series of patients data for the distal channel showed that most patients had abnormal findings: 80% when supine, 66% when upright, and 73% for total monitored time. For the proximal channel the readings were abnormal in 26% of patients for both supine and upright positions, and in 20% of patients for the total monitored time. This finding suggests that most of our patients (GERD, chest pain, globus sensation, etc) had evidence of reflux at the lower esophageal sphincter. Those with symptoms who did not have abnormal pH had symptoms of globus sensation, asthma, or atypical chest pain. Ambulatory pH monitoring was helpful in confirming pharyngeal symptoms due to reflux. Those patients with positive proximal findings in both supine and upright positions had more commonly symptoms related to the pharynx: heartburn (GERD) 75% and throat pain 25%. One patient with chest pain without positive findings on pH monitoring was found to have coronary artery disease on further angiographic evaluation.

Monitoring the total number of reflux events in a 24-hour period showed that two patients had more than 35 episodes. Both of these patients had GERD symptoms with hiatal hernia on x-ray evaluation and negative biopsies on flexible endoscopy.

In our series, ambulatory pH monitoring helped to establish a diagnosis in 75% of patients with atypical chest pain, 80% of patients with symptoms related to the pharynx (sore throat and globus), and 80% of patients with GERD. Four patients with negative biopsies on endoscopy had positive findings on pH monitoring. These findings are consistent with data reported by Klauser et al.[11]

Monitoring of pH is not routine in the evaluation of reflux. The study is performed in patients with continued symptoms after a trial of H2 blockers (normal doses) and in symptomatic patients with normal findings on imaging studies (upper gastrointestinal tract series or endoscopy). It is most helpful in patients with atypical chest or pharyngeal pain. When one considers the added costs of many clinical investigations without a diagnosis in this group of patients, pH monitoring is cost-effective.

CONCLUSION

Ambulatory pH monitoring is a relatively safe and cost-effective technique for evaluating patients with many different types of gastroesophageal and pharyngeal complaints that may be related to gastroesophageal reflux. The data, however, should be interpreted in the context of the symptom complex on presentation. Future areas of investigation will include the initial and follow-up studies with therapy.

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AURICULAR CARTILAGE GRAFTS IN LARYNGOTRACHEAL RECONSTRUCTION

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Introduction of the anterior cricoid split (decompression) and laryngotracheal reconstruction with costal cartilage graft has resulted in the successful management of many cases of subglottic stenosis. However, the procedure does not allow uniform extubation, and laryngotracheal reconstruction with costal cartilage may be too aggressive for neonates. We have explored the use of autogenous auricular cartilage graft in laryngotracheal reconstruction. Its high rate of success and low morbidity have enabled us to expand the indications. We report our experience in 23 patients with auricular cartilage grafts.

KEY WORDS — **anterior cricoid split, auricular cartilage graft, costal cartilage graft, laryngotracheal reconstruction, subglottic stenosis.**

INTRODUCTION

Introduction of surgical methods to treat subglottic stenosis over the last 15 years has allowed successful extubation or decannulation through single-stage and staged reconstructions.[1] The carbon dioxide surgical laser[2,3] and the pediatric urethral resectoscope[4,5] have been reported as successful in treating less severe cases of subglottic stenosis without using tracheotomy. Neither has gained widespread acceptance in the neonate. Cotton and Seid[6] introduced the anterior cricoid split (ACS; decompression) as an alternative to tracheotomy in premature infants. The indications for the ACS have been extended to include infants and children with mild subglottic narrowing. The failure rate of ACS is 22% to 23%.[4,7] The treatment of neonates with subglottic stenosis remains controversial.

Laryngotracheoplasty (LTP) with costal cartilage graft (CCG) was introduced by Fearon and Cotton[8] and is the mainstay of management of moderate to severe subglottic stenosis. This paper discusses a modification of LTP using autogenous auricular cartilage graft (ACG). The ACG has minimal donor site morbidity, causes minimal cosmetic deformity, and is a malleable cartilage that closely approximates the width of tracheal cartilage. When in place it can increase the diameter of the trachea to a greater extent than can the CCG.

PROCEDURE

The patient is anesthetized through an indwelling tracheotomy or endotracheal tube. The patient should undergo a direct rigid laryngoscopy and bronchoscopy before the reconstruction. If the stenosis is severe or long, an ACG will not be used. The patient is positioned with the neck extended, a shoulder roll in place, and both ears exposed. The mouth is draped out of the sterile field with a plastic drape. This will allow intraoperative laryngoscopy and bronchoscopy.

The neck is explored and a laryngofissure is performed to determine the extent of stenosis and length of cartilage needed. A horizontal incision is placed in the skin over the cricoid cartilage. The strap muscles are divided along the median raphe, and the cricoid,

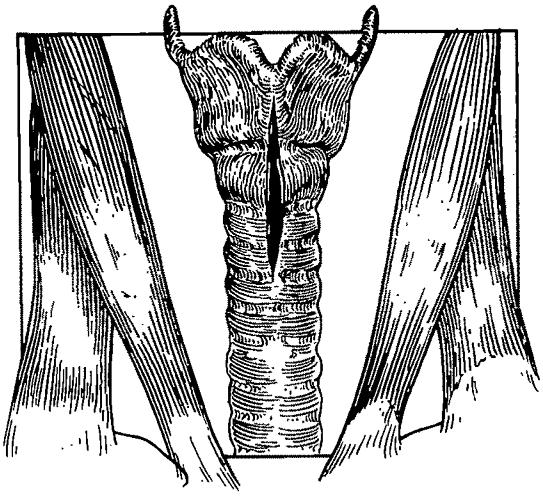

Fig 1. Diagram of incised trachea, cricoid, and thyroid cartilage.

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Desert, California, April 13-14, 1992.

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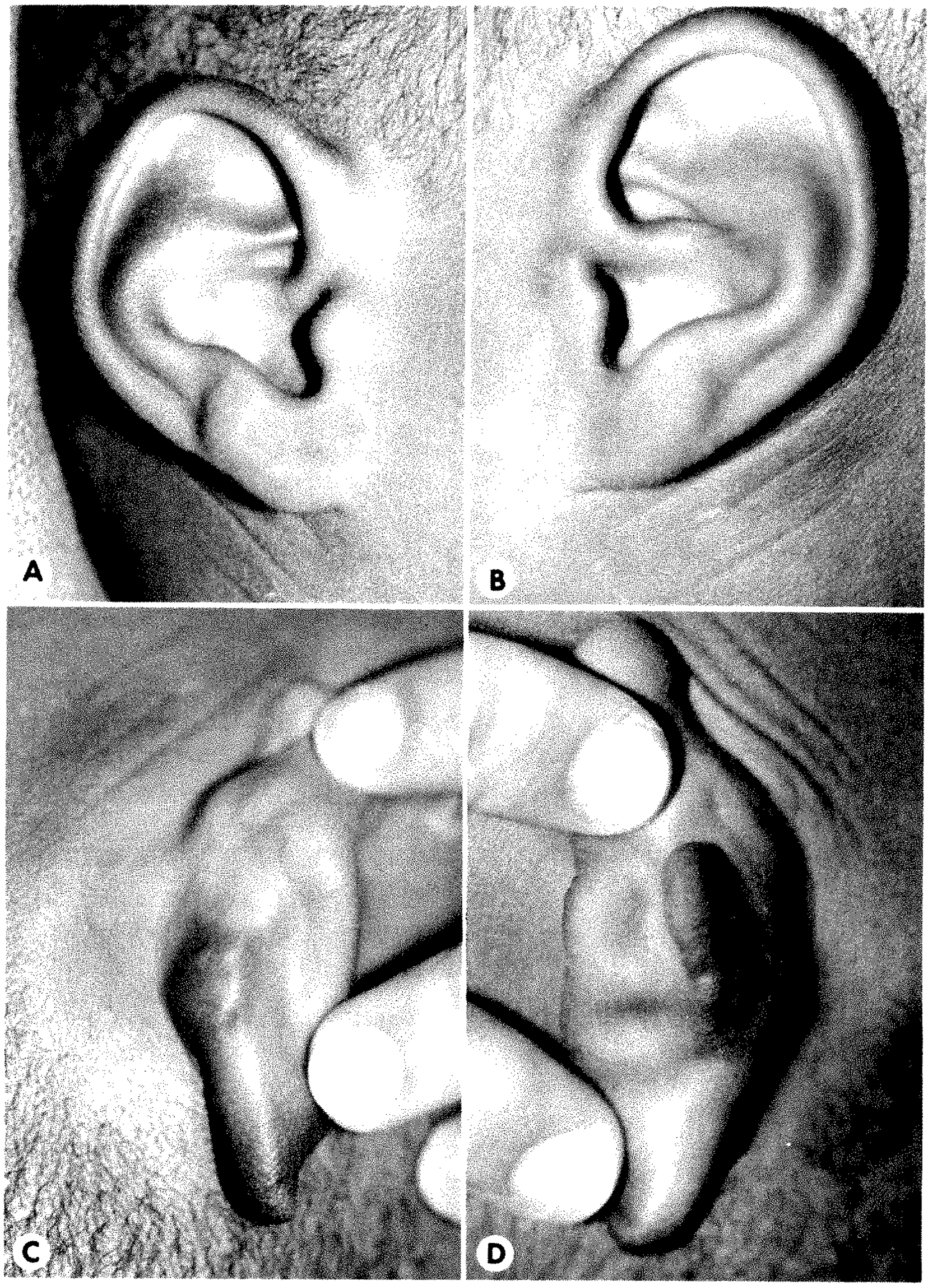

Fig 2. Four different auricles. A,B) Four years after cartilage harvest. C,D) With keloids that have formed along postauricular cartilage incision.

thyroid, and tracheal cartilage is exposed. A vertical midline incision is made through the cricoid cartilage, tracheal rings 1 and 2, and the lower third of the thyroid cartilage (Fig 1). The incision must be visualized endoscopically to ensure that the full length of the subglottic stenosis has been opened. The lumen of a narrow stenosis is best identified endoscopically with a 25-gauge needle placed through the trachea and into the lumen. The incision into the lumen of the stenosis can then be made relatively safely by using the needle as a guide. The length of stenosis and length of the required cartilage can then be assessed.

The auricular cartilage is harvested through a postauricular incision (Fig 2). Some colleagues have verbally reported the use of an anterior incision with minimal cosmetic deformity. We prefer to use a postauricular cartilage incision, particularly in black patients, because of the risk of keloid formation. The skin of the posterior auricle is infiltrated with 1% lidocaine with 1:100,000 epinephrine. A 25-gauge needle is dipped in methylene blue and used to mark the graft to be harvested (Fig 3). The area most frequently used is the cymba conchae. Through the postauricular incision the skin is elevated just superficial to the perichondrium and the cartilage tattoos are identified. An incision is made along the outlined auricular cartilage. The cartilage with the perichondrium is dissected from the anterior auricular skin. It is important to have perichondrium on both

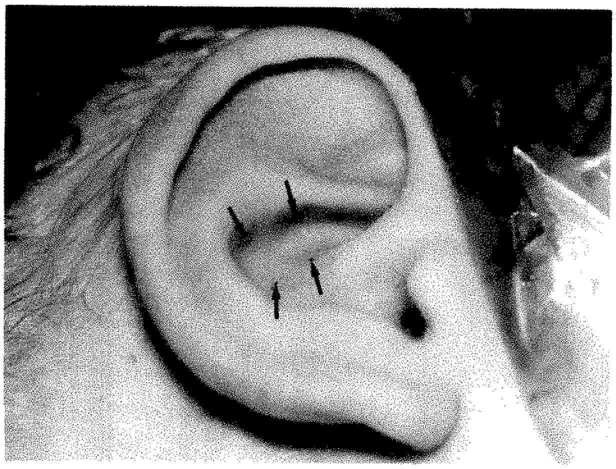

Fig 3. Auricular cartilage from cymba conchae being tattooed prior to being harvested from posterior incision.

sides of the cartilage. The wound is loosely approximated with interrupted 4-0 chromic subcuticular sutures over a rubber band drain. Cotton is placed in the concha and pressure is applied through a mastoid dressing.

A 4-0 Prolene or Vicryl suture is placed through the cricoid cartilage, just lateral to the incision, and tied through the strap muscles (Fig 4). This maneuver holds the cricoid incision open as wide as possible (Fig 5A,B). An opening of 3 to 4 mm can usually be created in this manner. We have not, to date, used a four-quadrant split with an ACG. The cartilage is cut in an elliptical shape to the desired length, with a width 30% to 40% greater than that of the ACS. Prior to being sutured in place, the auricular cartilage is pliable and has little strength. The thickness of the auricular cartilage is the same as the width of the tracheal cartilage. When the ACG is sutured into place, the graft forms an arch, giving the graft much greater rigidity and an increased cross-sectional area of the subglottis. The concave side of the graft should face the airway (Fig 5C). Suturing the auricular cartilage into the trachea can be technically challenging, as the cartilage alone is not strong enough to hold a suture. We have found it best to place the suture through the cartilage and the outer perichondrium. It is the perichondrium that holds the graft in place. The neck incision is closed in layers, with 3-0 and 4-0 interrupted chromic sutures. A small Penrose drain is placed to prevent trapping and dissection of air into the surrounding tissue. If a single-stage reconstruction is performed, the patient is intubated, sedated, and paralyzed in the intensive care unit. Repeat bronchoscopy is performed in 5 to 7 days to assess the status of the graft. If the repair is deemed satisfactory, we prefer to extubate the child in the intensive care unit when he or she is fully alert. We have extubated or decannulated some patients immediately in the operating room.

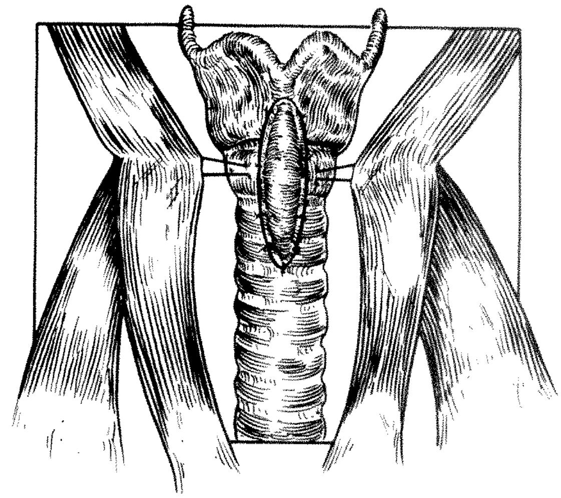

Fig 4. Sutures through cricoid cartilage for holding incision open and auricular cartilage sewn in place.

RESULTS

Table 1 summarizes case histories of 23 patients with acquired or congenital subglottic stenosis in whom we performed ACG-LTP. Twenty of the 23 patients were below the age of 2 at the time of presentation.

Seventeen of the 23 patients were successfully extubated or decannulated with one single-stage ACG-LTP. There were 8 ACSs (patients 1, 2, 4, 7, 14, 17, 19, and 20) that failed, and 5 of these patients (1, 2, 14, 19, and 20) were successfully treated with a single-stage ACG-LTP (Table 2). One of these ACG-LTPs (patient 4) failed. Two additional ACS failures (7 and 17) were treated with CCG-LTPs and both procedures failed. Of the three failed ACSs (4, 7, and 17), all resulted in long-term failures and multiple at-

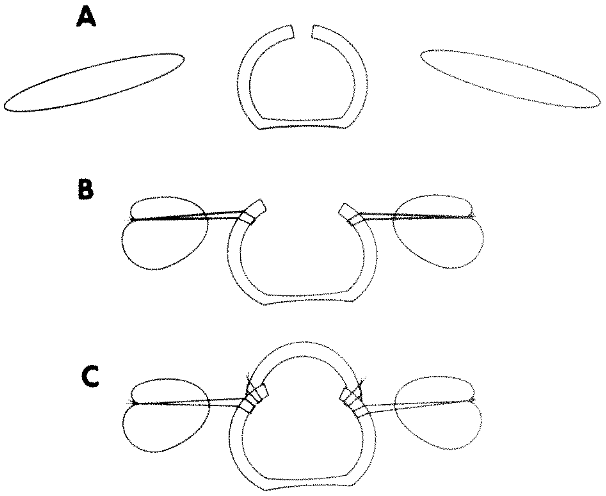

Fig 5. Diagrams of operation. A) Axial view of cricoid, which has been incised. B) Sutures placed through cartilage, but not through mucosa, and sutured to strap muscles. C) Auricular cartilage sewn in place.

TABLE 1. CASE SUMMARIES

Patient No.	*Stenosis Size*	*Procedure*	*Age*	*Stent Type*	*Duration*	*Complications*	*Success or Failure*	*Follow-up (y)*
1	Ulcer	ACS	3 mo	3.5 ET	7 d	Failed	F	
		ACG-LTP	4 mo	4.0 ET	13 d	None	S	3.7
2	Ulcer	ACS	1 mo	3.5 ET	7 d	Failed	F	
		ACG-LTP	5 mo	3.5 ET	7 d	None	S	2.5
3	Ulcer	ACG-LTP	6 mo	3.0 ET	4 d	None	S	2.7
4	<2.7 mm	ACS	3 mo	3.0 ET	7 d	Failed	F	
		ACG-LTP	3.5 mo	3.0 ET	13 d	Failed	F	
		CCG-LTP	18 mo	3.0 ET	7 d	Stenosis	F	2.0
5	<3.5 mm	ACG-LTP	12 y	None	0 d	None	S	2.8
6	<2.7 mm	Laser	9 mo	None	1 d	Stenosis	F	
		ACG-LTP	11 mo	4.5 ET	1 d	None	S	3.3
7	3 mm	ACS	2 mo	3.0 ET	7 d	Stenosis	F	
		CCG-LTP	2 y	Aboulker stent	6 mo	None, failed at 4 y	F	
		ACG-LTP	6 y	4.0 ET	7 d	None, failed at 2.5 y	S	
		CCG-LTP	6.5 y	Aboulker stent	3 mo	None, failed at 6 mo	F	2.6
8	<2.7 mm	ACG-LTP	4 mo	4.0 ET	7 d	None	S	2.5
9	<2.7 mm	ACG-LTP	15 mo	Aboulker stent	2 wk	Granulation tissue	S	2.5
10	3.6 mm	ACG-LTP	12 mo	3.5 ET	7 d	None	S	2.7
11	3.6 mm	ACG-LTP	9 mo	4.5 ET	7 d	Granulation tissue	F	4.0
	4.0 mm	ACG-LTP	3 y	4.5 ET	7 d	None	S	
12	3.5 mm	ACG-LTP	3.5 mo	3.5 ET	5 d	Web	S	2.3
13	3.5 mm	ACG-LTP	18 mo	4.0 ET	6 d	Granulation tissue	S	2.4
14	3.0 mm	ACS	1 mo	3.5 ET	7 d	None	F	
	3.0 mm	ACG-LTP	3 mo	3.5 ET	10 d	Pneumonia	S	1.6
15	3.0 mm	CCG-LTP	14 y	Aboulker stent	3 mo	Stenosis	F	
	3.0 mm	ACG-LTP	18 y	Aboulker stent	3 mo	Scar band	S	2.1
16	3.0 mm	ACG-LTP	19 mo	4.0 ET	6 d	None	S	2.4
17	1.5 mm	ACS	3 mo	2.5 ET	14 d	Stenosis	F	3.0
		Cast-LTP	1.7 y	Aboulker stent	1.5 mo	Stenosis	F	
		CCG-LTP	2.6 y	Aboulker stent	21 d	Stenosis	F	
		Cast-LTP	5.3 y	Aboulker stent	2 mo	Stenosis	F	
		ACG-LTP	5.9 y	Aboulker stent	1 mo	Stenosis, granulation tissue	F	2.8
18	<2.7 mm	Laser	2.5 y	None	0 d	Stenosis	F	
		CCG-LTP	2.6 y	Aboulker stent	3 mo	Abscess, stenosis	F	
		ACG-LTP	3.6 y	Aboulker stent	1 mo	None, failed at 1 y	F	
		CCG-LTP	4.7 y	Aboulker stent	1 mo	None	S	3.7
19	Ulcer	ACS	1 mo	3.5 ET	7 d	Stenosis	F	
		ACG-LTP	1 y	4.0 ET	7 d	None	S	0.7
20	Ulcer	ACS	6 mo	3.5 ET	8 d	None, failed at 9 d	F	
		ACG-LTP	7 mo	3.5 ET	8 d	None	S	1.3
21	<2.7 mm	CCG-LTP	2.7 y	Aboulker stent	1 mo	None	F	
		CCG-LTP	3 y	Aboulker stent	4 mo	None, failed at 1.5 y	F	
		ACG-LTP	6 y	6.0 ET	13 d	None	S	4.5
22	<2.7 mm	ACG-LTP	1.4 y	4.0 ET	7 d	None	S	0.4
23	<2.7 mm	ACG-LTP	3 mo	4.5 ET	7 d	None	S	1.7

F — failure, S — success, ACS — anterior cricoid split (decompression), ACG-LTP — auricular cartilage graft laryngotracheoplasty, CCG-LTP — costal cartilage graft laryngotracheoplasty, Cast-LTP — castellated laryngotracheoplasty, ET — endotracheal tube (size).

TABLE 2. OUTCOME OF AURICULAR CARTILAGE GRAFTS AND ESTIMATED DEGREE OF STENOSIS

Primary Procedure	*Secondary Procedure*	*Success or Failure*	*Patient No.*	*Size (mm)*	*Grade*
8 ACS	6 ACG-LTP	S	1, 2, 19, 20	Ulcerated	NA
			14	3.0	2
		F	4	2.7	3
	2 CCG-LTP	S	None		
		F	7	3.0	2
			17	<2.7	3
12 ACG-LTP		S	5, 10, 11, 12	3.5	2
			3, 15, 16	3.0	2
			6, 8, 9	<2.7	3
			22, 23	<2.7	2
		F	None		
3 Multiple procedures		S	18, 21	<2.7	3
			15	3.0	2
		F	None		

ACS — anterior cricoid split (decompression), ACG-LTP — auricular cartilage graft laryngotracheoplasty, CCG-LTP — costal cartilage graft laryngotracheoplasty, NA — not applicable.

tempts to reconstruct the airway. Twelve patients (3, 5, 6, 8, 9, 10, 11, 12, 15, 16, 22, and 23) had primary single-stage ACG-LTPs that resulted in successful extubation. A total of 7 patients (4, 7, 11, 15, 17, 18, and 21) had multiple LTPs. Four of the ACG-LTPs (patients 11, 15, 18, and 21) were successful and 3 (4, 7, and 17) were failures. Two of these patients remain tracheotomy-dependent (7 and 17) and 1 has died (4). Table 3 summarizes the multiple procedures in their order of performance. According to the immediate results, there were 19 of 23 (83%) successful ACG-LTPs and 4 of 23 (17%) failures (4, 12, 14, and 17). All 4 of the failures were followed with multiple procedures.

One child (patient 5) had congenital subglottic stenosis with recurrent croup severe enough to have required an emergent tracheotomy at another institution. This patient was repaired with an ACG-LTP and extubated at the time of the repair. In the other 22 patients, subglottic stenosis was believed to be secondary to injury from endotracheal intubation.

Granulation tissue was encountered at the lower site of the graft in four patients (9, 11, 13, and 17). This was managed successfully with endoscopic excision. One patient (11) had significant granulation tissue at the lower anastomosis, and this required a second ACG-LTP. It should be noted that the first ACG-LTP was widely patent.

DISCUSSION

Until recently, we used the ACS and CCG-LTP as the mainstays of repair of moderate to severe subglottic stenosis. As reported by others,[2-13] we have found the ACS to be effective in managing many cases of mild subglottic stenosis. Holinger et al[3] found an overall success rate of 71% for primary ACSs and 85% for secondary ACSs. Possible mechanisms for the success of the ACS include springing open of the cricoid cartilage, leading to an increase in the cross-sectional area of the subglottic lumen. This could restore circulation to the mucosa, decrease the mucosal edema, and possibly drain subglottic cysts. None of these mechanisms have been definitely established.[3] Holinger et al[3] observed that only a small gap opens in the cricoid cartilage after it has been

TABLE 3. PATIENTS WITH MULTIPLE PROCEDURES IN ORDER OF OCCURRENCE AND EVENTUAL OUTCOME

	Procedures					
Pt No.	*1*	*2*	*3*	*4*	*5*	*Outcome*
4	ACS	ACG-LTP	CCG-LTP			Died
7	ACS	CCG-LTP	ACG-LTP	CCG-LTP		Failed
11	ACG-LTP	ACG-LTP				Success
15	CCG-LTP	ACG-LTP				Success
17	ACS	Cast-LTP	CCG-LTP	Cast-LTP	ACG-LTP	Failed
18	CCG-LTP	ACG-LTP	CCG-LTP			Success
21	CCG-LTP	CCG-LTP	ACG-LTP			Success

ACS — anterior cricoid split (decompression), CCG-LTP — costal cartilage graft laryngotracheoplasty, ACG-LTP — auricular cartilage graft laryngotracheoplasty, Cast-LTP — castellated laryngotracheoplasty.

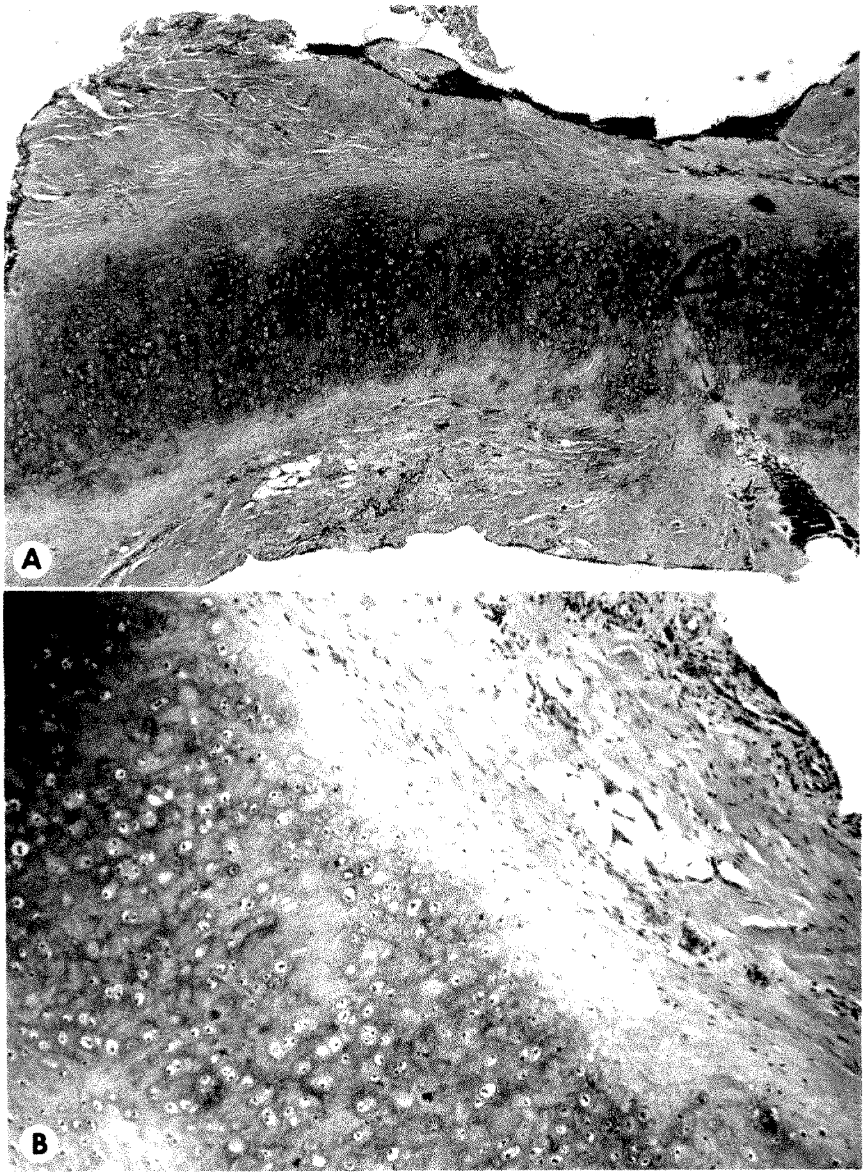

Fig 6. Implanted auricular cartilage that had been in place for 14 months (patient 4). Note minimal absorption. A) Low-power view. B) High-power view.

split. They also found that the cut ends of the cricoid cartilage were closely approximated in postmortem specimens.

There are, however, children who fail an ACS and require more aggressive surgical management. There is reluctance to perform CCG-LTP as a first-stage procedure because of possible morbidity with harvesting a CCG.[14] To overcome this potential donor site morbidity in neonates, we started using auricular cartilage from the cymba conchae. The auricular donor site causes minimal deformity and morbidity. Initially, we reserved the ACG-LTP for patients who failed the ACS; however, with our successful experience we began to use auricular cartilage as a primary single-stage procedure. We have also combined the ACG and Aboulker stents in children with moderate to severe subglottic stenosis, with limited success.

The techniques employed in this procedure are not new. Suturing the trachea to the sternocleidomastoid muscle had already been used by European surgeons to treat tracheomalacia.[15,16] We do not feel that these sutures to the strap muscles hold the subglottis open for an extended time. It is more likely that the subglottic incision is held open primarily by the auricular cartilage.

Free ACGs were first used for tracheal and subglottic reconstruction around the turn of the century.[17] An auricular cartilage free graft was used in 1950 by Caputo and Consiglio[18] to successfully repair a tracheal stenosis. Meyer[19] implanted auricular cartilage beneath the buccal mucosa and harvested both mucosa and cartilage a few weeks later. He then used the composite graft to repair the tracheal wall. Zehm[20] used a composite skin graft and ACG to successfully treat three patients with stenosis of the "laryngotracheal zone." We have not used composite

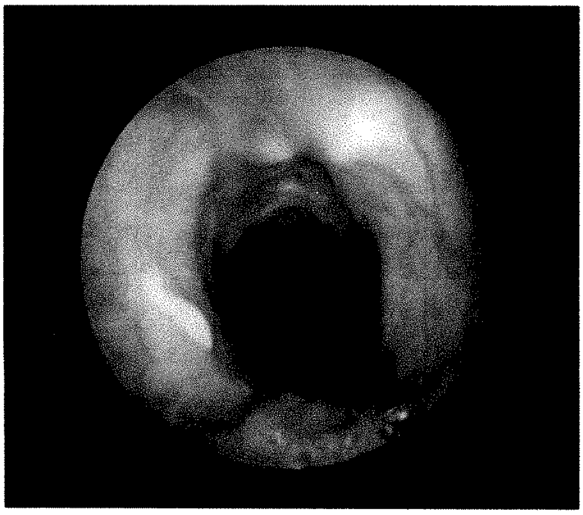

Fig 7. Subglottis 4 years after placement of auricular cartilage graft. Note excellent lumen and apparent growth of subglottis.

grafts, because the epithelium appears to rapidly cover over the auricular cartilage perichondrium. Zalzal et al[21] noted that CCGs remain viable in rabbits. The best results were obtained when the perichondrium was left on the intraluminal side. One of our patients, in whom a CCG was placed after an ACG, provided an opportunity to perform a biopsy on an ACG that had been in place for 14 months (Fig 6). There was good viability of the ACG, with little absorption. We have also observed a graft 4 years after placement (Fig 7), and the cartilage has apparently grown and the patient has a widely patent lumen.

We have noted reepithelialization of the auricular cartilage graft, but do not know how long complete reepithelialization actually takes. The epithelialization is far from complete at 7 days. A small area of pedunculated granulation tissue that formed in four patients (9, 11, 13, and 17) was thought to be secondary to an exposed polydioxanone suture. Friedman et al,[22] however, found polydioxanone suture to be superior to Vicryl when used in the trachea.

The auricular cartilage closely approximates the thickness of tracheal cartilage. When sewn in place it has considerable rigidity and strength similar to that of the trachea. The auricular cartilage perichondrium provides a surface for epithelialization that limits the amount of granulation tissue. The arched shape of the graft adds cross-sectional area to the subglottis that helps to ensure a successful repair. The arched shape of the graft also resists prolapse of the cartilage into the tracheal lumen.

We prefer to use the ACG-LTP for mild to moderate subglottic stenosis or failed ACSs. Unfortunately, we cannot identify which patients would benefit from a primary ACG-LTP instead of an ACS. We have become more liberal about performing primary ACG reconstruction instead of ACS. The single-stage reconstruction is preferred, as it prevents the use of a tracheotomy. We believe we have prevented multiple procedures in some patients. We have relied on clinical judgment to help determine which cases would benefit from primary ACG-LTP. The morbidity for ACG-LTP is so low that we think it can be aggressively used. It does not appear that the estimated narrowness or grade of stenosis, as described by Cotton et al,[23] predicts failure of the ACG (Table 2).

Although we have had some success in using ACG-LTP in more severe subglottic stenosis, we would not recommend auricular cartilage for severe or long-segment stenosis. The stenosis should be short enough to allow a single ACG to span its length. A limiting factor, therefore, is the length of the auricular cartilage available.

In conclusion, infants and children with mild to moderate short subglottic stenoses can be successfully treated with ACG-LTP. Auricular grafts have the potential of creating a lumen of greater diameter than a CCG. It is a procedure that can be used for subglottic or tracheal reconstruction. The ACG can increase the success of single-stage reconstructions, with morbidity and mortality rates comparable to those of the ACS.

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PEDIATRIC AIRWAY ENDOSCOPY COURSE

The postgraduate Pediatric Airway Endoscopy Course will be held May 5-8, 1993, at St Louis Children's Hospital, St Louis, Missouri. For further information, contact Marilyn Crawshaw at (314) 454-2138. The course will also be held November 3-6, 1993, at The Children's Memorial Hospital, Chicago, Illinois. For further information, contact Geri Miseska at (312) 880-4457.

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STROBOSCOPIC VIDEOLARYNGOSCOPY: A COMPARISON OF FIBERSCOPIC AND TELESCOPIC DOCUMENTATION

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The clinical value of stroboscopic videolaryngoscopy (SVL) for the evaluation of laryngeal disorders has been emphasized. Some investigators advocate the use of a flexible fiberscope, while others recommend the use of a rigid telescope for SVL. In order to determine which procedure is more useful for clinical diagnosis, the senior author (E.Y.) performed both fiberscopic and telescopic SVL on 120 consecutive patients who complained of hoarseness. Equipment used included the Olympus ENF-P3 fiberscope, the Nagashima SFT-1 rigid telescope, the Nagashima LS-3A laryngostroboscope, and color video cameras. Our study indicated that stroboscopic images produced by telescopic SVL were superior to those from fiberscopic SVL in the majority of cases. The purpose of this paper is to compare fiberscopic and telescopic SVL, to evaluate the advantages and disadvantages of fiberscopic and telescopic SVL, and to present the authors' recommendations.

KEY WORDS — fiberscopic strobovideolaryngoscopy, stroboscopic videolaryngoscopy, telescopic strobovideolaryngoscopy.

INTRODUCTION

Noninvasive voice analysis has revolved around measurements of vibratory, acoustic, and aerodynamic characteristics.[1] Stroboscopy is an integral part of assessment of vocal function in the clinical voice laboratory[2-4] and has proven to be one of the most useful methods for evaluating the vibratory movements of the vocal folds (cords).[5-7] With the remarkable advances in video and optical technology, it became possible to simultaneously document laryngeal images and voice.[8,9] Stroboscopic findings of the larynx can now be easily documented.[1-7]

High-speed motion photography was first used to demonstrate vocal fold movement during phonation in a motion picture produced by the Bell Laboratories in 1937.[10] Subsequent studies were performed by Timke et al[11,12] and von Leden et al[13] in the 1950s, and by Koike,[14] to further refine this technique of laryngeal visualization. This technique suffered, however, from the need for expensive equipment, the large amount of film needed (5,000 frames per second), and an extremely time-consuming analysis.

Stroboscopic examination of the larynx was first performed in 1878 by Oertel,[15] who utilized a rotating disc, spinning in synchrony with the patient's phonatory frequency, to "freeze" the laryngeal image during indirect laryngoscopy. Further studies on laryngostroboscopy were done by Kallen[16] and Powell.[17] With the introduction of electronic stroboscopy, great strides were made in developing and establishing the diagnostic value of stroboscopy.[18-28]

Precise evaluation of vocal fold vibration, includ-

DIAGNOSES MADE AT TIME OF STROBOSCOPY

Diagnosis	
Chronic laryngitis	29
Vocal fold polyp (preoperative and postoperative)	28
Laryngeal carcinoma (preoperative and postoperative)	15
Reinke's edema (preoperative and postoperative)	13
Vocal fold paralysis	9
Vocal fold nodule	7
Hypertrophied lingual tonsils	6
Recurrent laryngeal papillomatosis	4
Leukoplakia	3
Vocal fold hemorrhage	2
Gastroesophageal reflux laryngitis	2
Spastic dysphonia	2
Epiglottic cyst	2
Vocal fold and ventricular cyst	2
Vallecular cyst	1
Isshiki thyroplasty (postoperative)	1
Thyroid lymphoma	1
Aphonia	1
Vocal fold hemangioma	1
Arytenoid dislocation	1
False vocal fold lesion	1
Granuloma	1
Acute laryngitis	1
Contact ulcer	1
Teflon injection (postoperative)	1
Subglottic cyst	1
Subglottic stenosis	1
Laryngocele	1
Hemorrhagic telangiectasia	1
Total	139

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Desert, California, April 13-14, 1992.

REPRINTS — Eiji Yanagisawa, MD, 98 York St, New Haven, CT 06511.

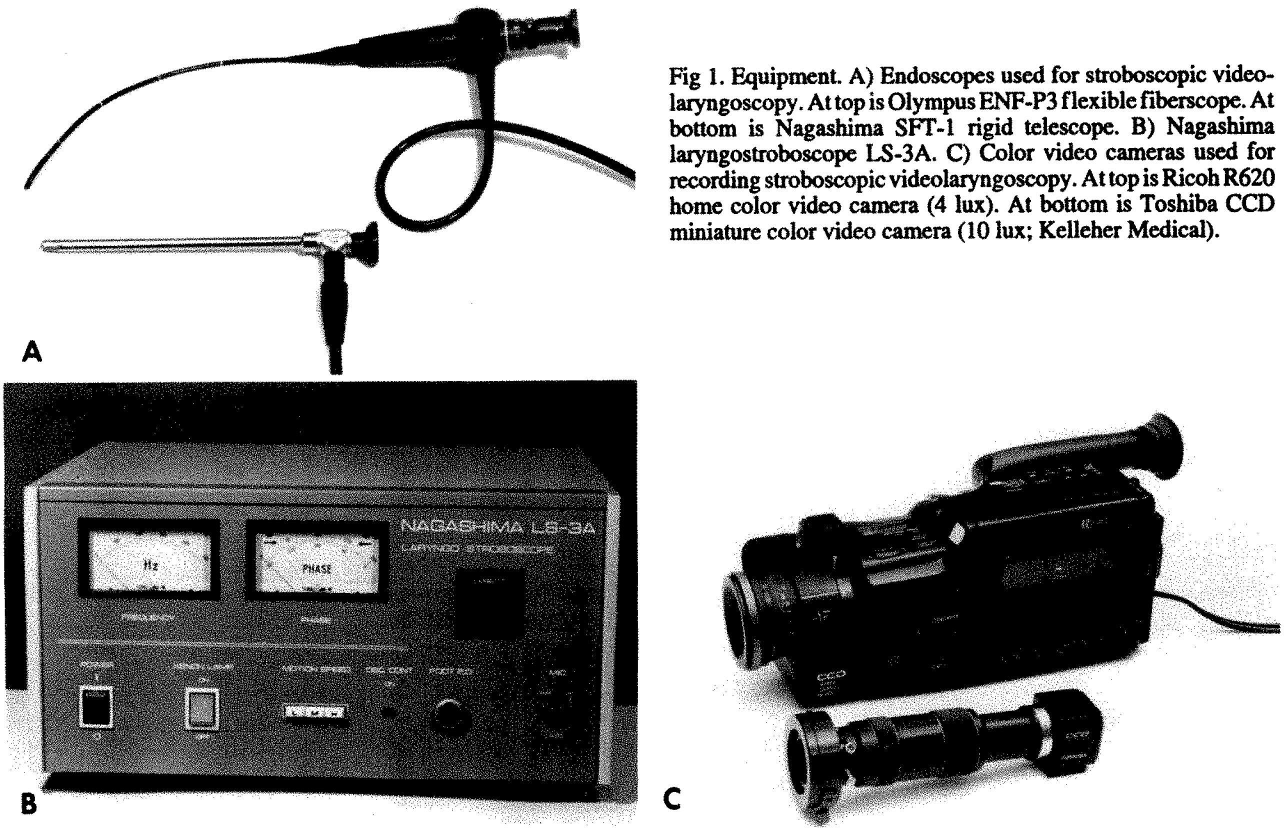

Fig 1. Equipment. A) Endoscopes used for stroboscopic videolaryngoscopy. At top is Olympus ENF-P3 flexible fiberscope. At bottom is Nagashima SFT-1 rigid telescope. B) Nagashima laryngostroboscope LS-3A. C) Color video cameras used for recording stroboscopic videolaryngoscopy. At top is Ricoh R620 home color video camera (4 lux). At bottom is Toshiba CCD miniature color video camera (10 lux; Kelleher Medical).

ing measurements of the amplitude, mucosal wave, and glottic closure, as well as pathologic conditions including early vocal fold carcinoma, can be made.[7,20] Hirano[6] introduced the "body-cover" theory of voice production. His theory contributed greatly to the understanding of vocal fold vibration as seen by stroboscopy.

The basis of stroboscopic examination is to produce rapid pulses of light that illuminate consecutive points along the vocal fold cycle. If the illumination flashes more frequently than every 0.2 seconds, the human eye processes these images into a continuous, "slow-motion" sequence. This occurs because of Talbot's law, which states that once an image is presented to the eye, it persists on the retina for 0.2 seconds. The perceived motion is an optical illusion created by fusing multiple points of several successive vibratory cycles. In contrast, high-speed photography records multiple points within the same vibratory cycle.[5,7]

Sawashima and Hirose[29] were the first investigators to use the flexible fiberscope for laryngeal examination, and the fiberscope is now incorporated as a part of the otolaryngologist's routine instrumentation.[9] The use of the modern rigid telescope for laryngeal examination was advocated by Ward et al,[30] Andrews and Gould,[31] Steiner and Jaumann,[32] Yanagisawa et al,[8] and others.[3,7,9,22,33] The value of videographic documentation of laryngoscopy (videolaryngoscopy) was emphasized by Yanagisawa et al,[8,9,33] Selkin,[34] and Yamashita.[35]

Some investigators advocate the use of a flexible fiberscope,[21,23,27,36] while others recommend the use of a rigid telescope[3,24,37] for stroboscopic videolaryngoscopy (SVL). Hirano et al[23] and Yoshida et al[36] initially advocated telescopic videostroboscopy, but in later publications, they favored the use of a fiberscope for SVL. In order to determine which procedure is more useful for clinical diagnosis, the senior author (E.Y.) performed both fiberscopic and telescopic SVL at the same sitting on 120 consecutive patients who complained of hoarseness. The same video cameras and laryngostroboscope were used for all of the patients included in this study. The purpose of this paper is to compare the advantages and disadvantages of fiberscopic and telescopic documentation of SVL and to present the authors' recommendations.

MATERIALS AND METHODS

SUBJECTS

A series of 120 consecutive patients who presented

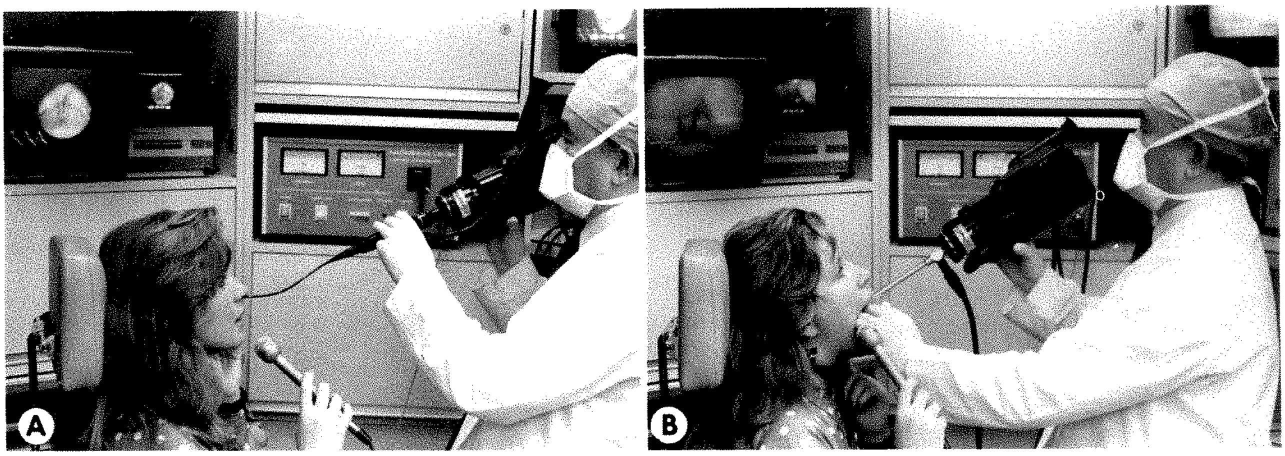

Fig 2. Technique of stroboscopic videolaryngoscopy (SVL) using Ricoh R620 video camera. A) SVL using Olympus ENF-P3 fiberscope. B) SVL using Nagashima SFT-1 rigid telescope.

with complaints of hoarseness from June 1991 to December 1991 were evaluated with both fiberscopic and telescopic SVL. A total of 134 endoscopies were performed on these 120 different patients. The age ranged from 19 to 95, with a mean age of 58.5. Sixty patients were male, and 60 were female. The distribution of disorders seen is summarized in the Table. Twenty-nine different diagnoses were made, for a total of 139 diagnoses. The most common diagnoses were chronic laryngitis, vocal fold polyps, and laryngeal carcinoma.

EQUIPMENT

In this study, the following equipment was used: 1) Olympus ENF-P3 3.4-mm flexible fiberscope (Olympus Corporation, Lake Success, NY; Fig 1A, top), 2) Nagashima SFT-1 rigid telescope (Kelleher Medical, Richmond, Va; Fig 1A, bottom), 3) Nagashima laryngostroboscope, model LS-3A (Fig 1B), 4) Ricoh R620 home color video camera (4 lux) with Karl Storz quick-connect adapter (Fig 1C, top), 5) Toshiba (Nagashima) CCD miniature color video camera (10 lux) with a 30- to 70-mm zoom lens adapter (Kelleher Medical; Fig 1C, bottom), 6) Sony 3/4-in VO-5600 and VO-9600 video recorders (Sony Corporation), 7) color television monitors, 8) Sony UP-5000 Mavi-graph color video printer, and 9) Electro-voice RE-10 unidirectional microphone. The Kay Elemetrics laryngograph model 6094 and Kay computer model 9140 (Kay Elemetrics, Pine Brook, NJ) were used in some cases.

TECHNIQUE

The patient sat upright facing the standing examiner. Each patient was prepared with 3% ephedrine sulfate and 4% lidocaine hydrochloride (Xylocaine) sprays applied intranasally to the nasal and nasopharyngeal mucosa, and 4% lidocaine solution applied intraorally to the soft palate, posterior tongue, and hypopharynx.[9,33]

Fiberscopic Strobovideolaryngoscopy. The flexible fiberscope, attached to the Nagashima laryngostroboscope and the Ricoh R-620 home video camera, was first passed through the wider nasal passage down to the larynx (Fig 2A). When the desired image was visualized on the television monitor, the laryngeal image was centered and sharply focused, and videotape recording was started. The patient was instructed to hold the laryngophone lightly against the lateral aspect of the thyroid cartilage with one hand (for measuring the fundamental frequency of the voice), and to hold a separate unidirectional microphone in front of the mouth with the other hand for obtaining high-quality voice recordings. In some cases, laryngeal waveforms were generated by the Kay laryngograph by using two additional laryngophones secured with a Velcro strap on both sides of the thyroid cartilage.

Telescopic Strobovideolaryngoscopy. After completion of the fiberscopic SVL, the telescopic SVL examination was performed at the same sitting (Fig 2B). The Nagashima SFT-1 (70°) telescope was connected to the video camera and the Nagashima laryngostroboscope. The tip of the rigid telescope was dipped in warm water to prevent fogging of the lens during the procedure. While holding the patient's tongue with one hand, the examiner inserted the telescope into the mouth. The telescope was passed along the midline of the upper surface of the tongue, along the glossoepiglottic fold, and beyond the upper surface of the epiglottis. The tip of the telescope was tilted in such a way that the entire vocal folds could be visualized. The 70° telescope allowed excellent visualization of both the anterior and posterior commissures. When the desired laryngeal image was seen on the monitor, video recording was begun. As in the fiberscopic examination, the patient held both the

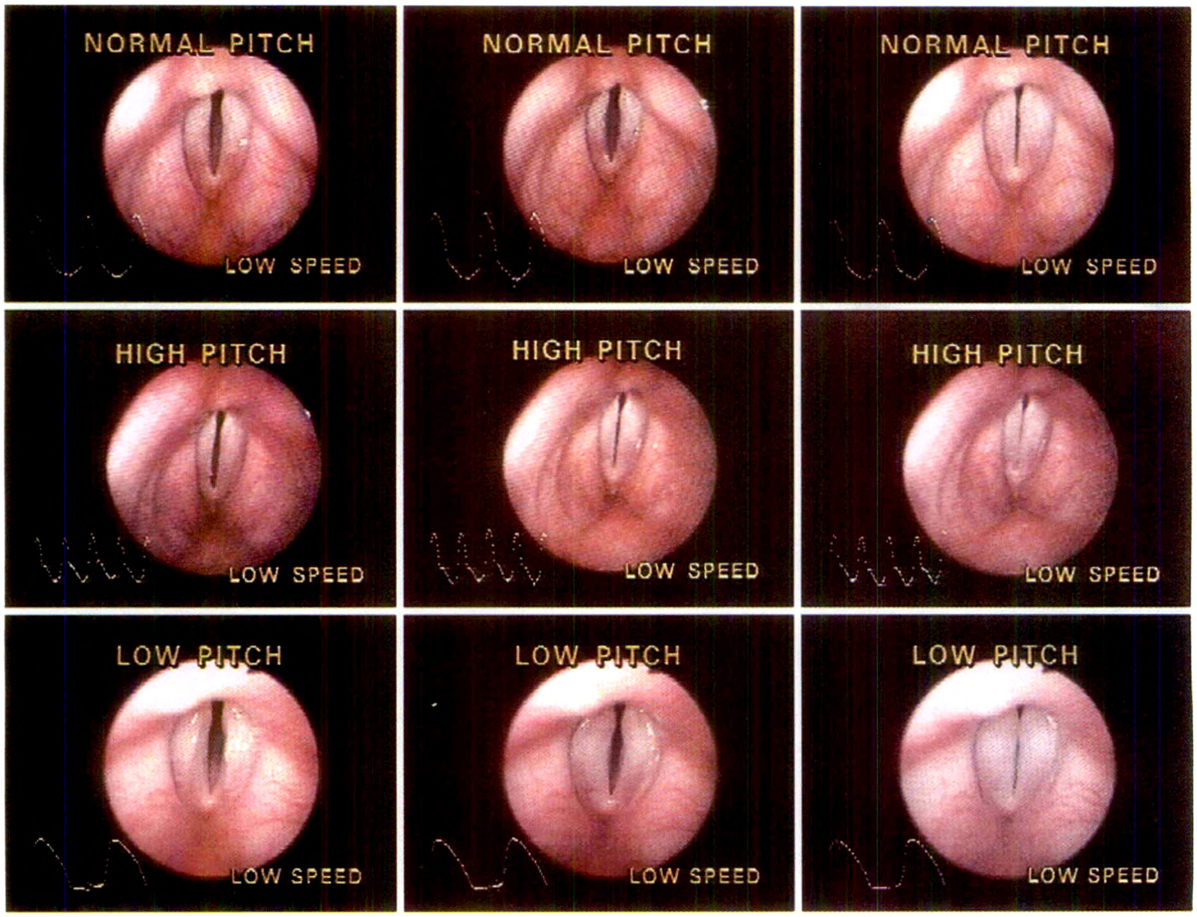

Fig 3. Fiberscopic SVL images. Top row shows normal pitch, middle row high pitch, and bottom row low pitch. Note small and grainy images obtained with fiberscope.

laryngophone and the separate microphone.

For both fiberscopic and telescopic examinations, stroboscopic evaluation was performed during phonation of sustained vowel /i/ at three different pitches (high, normal, low) and at normal loudness. In most patients, stroboscopic vocal fold vibration was also examined at different slow motion speeds (high, middle, low) by using the slow motion speed select push buttons on the Nagashima LS-3A. For fiberscopic examinations, stroboscopic evaluation also included counting from 1 to 10 at normal pitch and loudness.

Each of the videotape recordings was critically reviewed by the authors. They had been made on a Sony VO-5600 video recorder and were reviewed with a Sony VO-9600 video recorder that provided playback speed (slow motion) control. Comparisons of representative images from fiberscopic and telescopic SVL were made at the same pitch and same loudness level (in most cases, normal pitch and normal loudness). High-pitch stroboscopic images were not used for comparison, because they stretched the vocal folds and produced insufficient mucosal waves and amplitudes. Evaluation sheets were used to assess technical ease; image quality, including color, resolution, and brightness; degree of distortion; abnormal findings (including arytenoid and epiglottis configuration); and diagnostic value, with scores assigned in a scale of 1 through 4 (1 poor, 2 good, 3 very good, 4 excellent). Ratings of stroboscopic findings included measurements of symmetry, glottic closure, amplitude, mucosal wave, ventricular visualization, nonvibratory segments, and vertical level.[5] Hard copies of representative stroboscopic images of each patient were made with the Sony UP-5000 color video printer and taped to the evaluation sheets for comparative study.

RESULTS

A comparison was made between the stroboscopic examinations provided by the flexible fiberscope and rigid telescope. Technical ease, image quality, degree of distortion, findings, and diagnostic value were evaluated.

TECHNICAL EASE

In the majority of cases, both fiberscopic and rigid telescopic examinations were well tolerated. Out of 120 patients, difficulty in performing the procedure

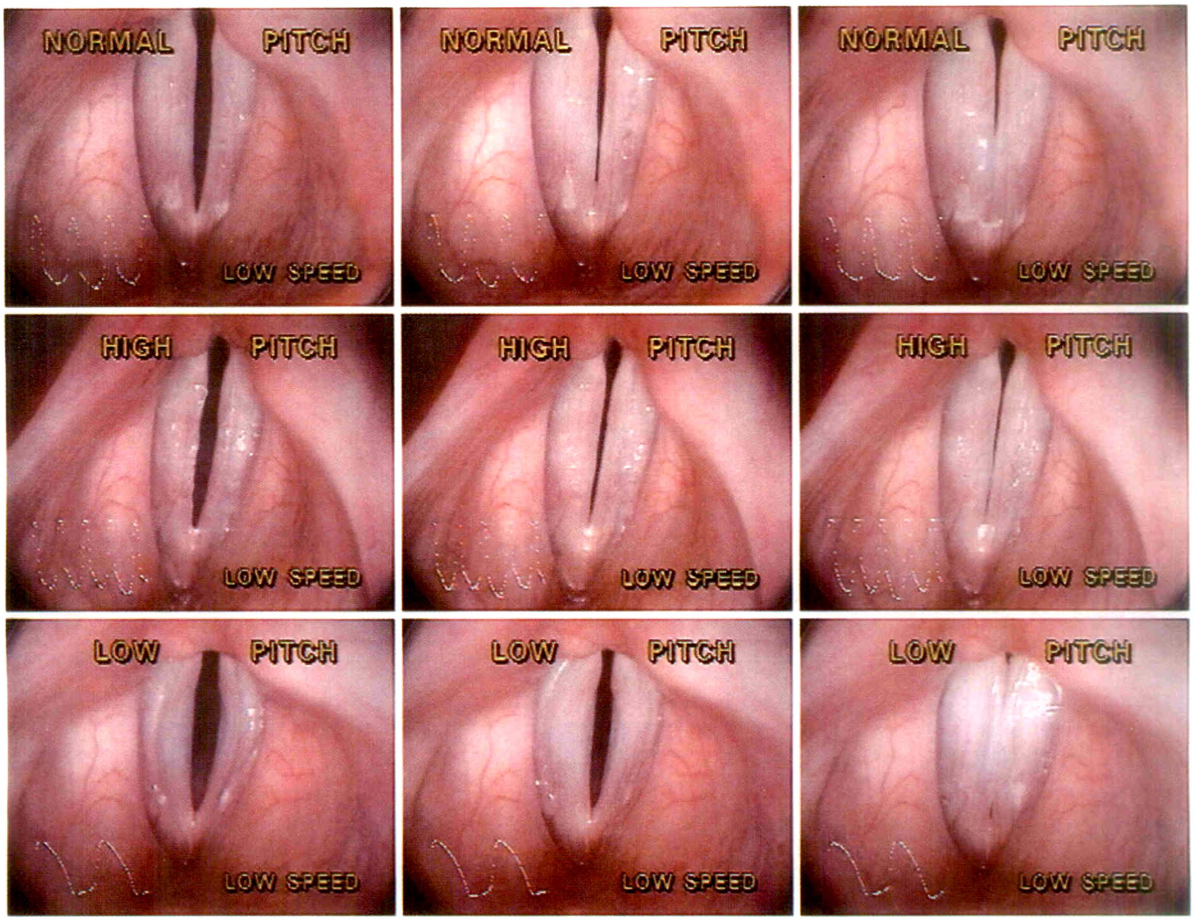

Fig 4. Telescopic SVL images. Top row shows normal pitch, middle row high pitch, and bottom row low pitch. In contrast to fiberscopic images of Fig 3, telescopic images are larger and clearer and have excellent color and resolution.

was encountered in 1 patient using the fiberscope, and 4 patients using the telescope. In 4 patients, the telescopic examination could not be performed because of hyperactive gag reflexes. There were no unsuccessful fiberscopic examinations. The difficulties that were encountered were all related to hyperactive gag reflexes.

IMAGE QUALITY

The quality of the stroboscopic images obtained with the rigid telescope was consistently better than that of the flexible fiberscope (Figs 3-5). Since the telescope delivers more light, the images tended to be brighter and of higher resolution. Often, the resolution of the fiberscope was limited by the light fibers themselves. Additionally, when a light fiber was damaged, it was seen as a disturbing black spot on the stroboendoscopic image.

The most informative and useful fiberscopic images were obtained when the tip of the fiberscope was positioned just above the level of the vocal folds. This created a larger image of the vocal folds on the video monitor, providing better visualization of mucosal waves and other stroboscopic parameters. When the fiberscope was not advanced to this level, the vocal folds appeared small and often hidden by the arytenoids, making it difficult to evaluate the stroboscopic findings.

The color reproduction was consistently better with the rigid telescope system (Fig 4). The colors retained a fairly natural hue when the Nagashima laryngostroboscope was used.

DISTORTION

Optical Factors. The fiberscopic view showed more distortion due to optical factors (Fig 6). When the tip of the fiberscope was advanced too close to the glottis, the laryngeal images appeared bigger in the center and smaller at the periphery, giving distorted stroboscopic images of the vocal folds and their mucosal waves. This optical distortion resulted from the wide-angle effect of the fiberscope lens.

Anatomic Factors. The fiberscopic view often showed a distorted image (Fig 6), because the fiberscope tip was inserted through a narrow nasal cavity with a septal deviation or a hypertrophied turbinate and tended to remain in a relatively lateral position in the hypopharynx. This led to a perceived stroboscop-

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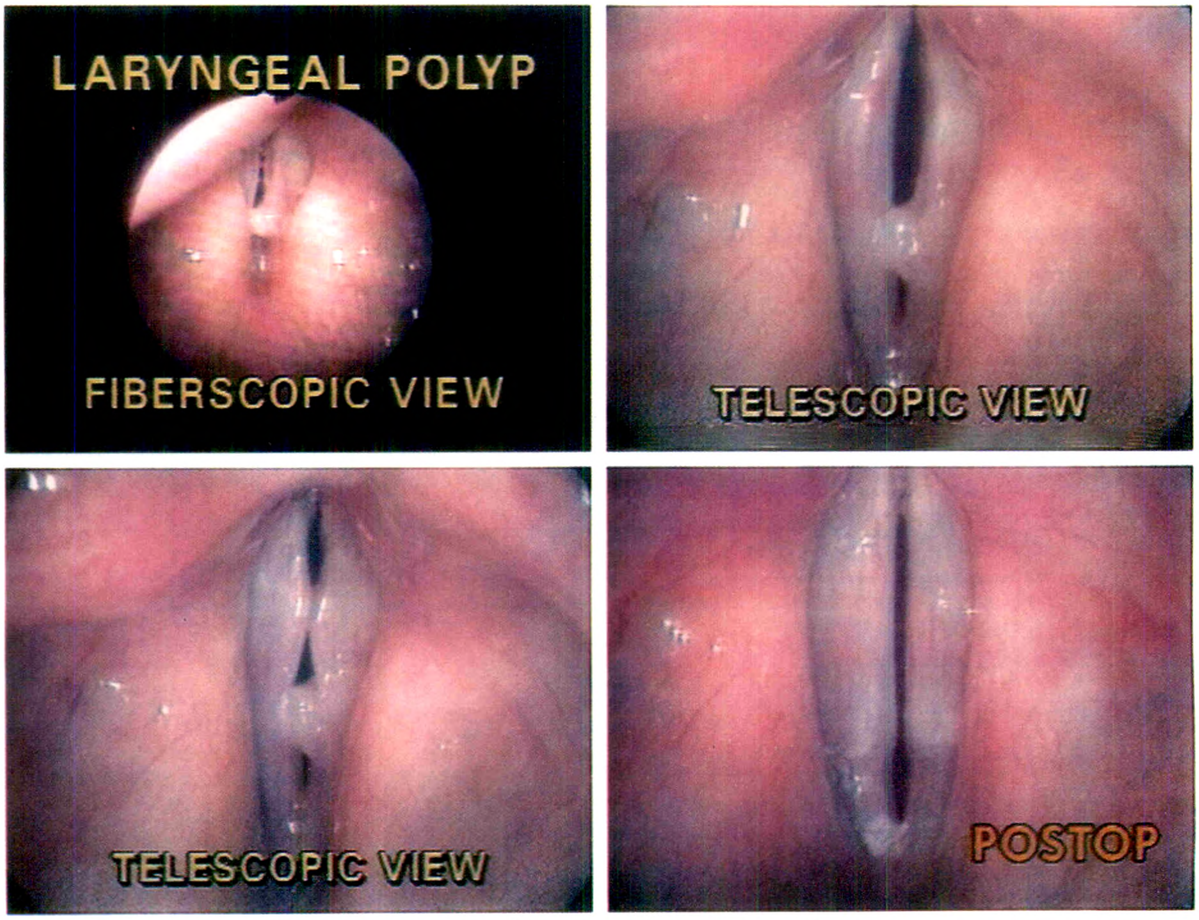

Fig 5. Laryngeal polyp on normal-pitch phonation.

ic asymmetry in size of the vocal folds and supraglottic structures. In patients with septal deviations or septal spurs or hypertrophied turbinates, it was difficult or impossible to adjust the angulation of the fiberscope tip to eliminate the distortion.

Technical Factors. The telescopic system provided minimal distortion as long as the telescope was positioned in the midline of the tongue and oropharynx (Fig 6). If the telescope was positioned lateral to the midline or was swiveled on a horizontal axis, distortion in size of the vocal folds was noted, with one vocal fold appearing larger than the other. The glossoepiglottic fold serves as an excellent marker for midline positioning during telescopic examinations (Fig 6).

DIAGNOSTIC VALUE

Both the flexible fiberscope and the rigid telescope provided good to excellent visualization of the larynx and surrounding structures. The fiberscope was noted to demonstrate the ventricles better than the telescope. Additionally, since the tip of the fiberscope could be advanced to the level of the glottis, the fiberscope provided a better evaluation of the subglottic region. Inadequate anesthesia led to supraglottic stimulation, and vigorous coughing in two patients.

Overall, the telescope was judged to provide better visualization and diagnostic value of vocal fold vibration than the fiberscope. Although stroboscopic parameters such as symmetry, glottic closure, amplitude, mucosal wave, visibility of the ventricle, and nonvibrating segment were documented, our data were primarily based on image quality and visibility of the entire vocal folds and their vibratory patterns and mucosal waves. Each method was rated on a scale of 1 to 4. In 113 cases (84.3%) the telescope received a higher rating than the fiberscope. In 11 cases (8.2%) the telescope and fiberscope were equal in diagnostic value. In 10 cases (7.5%) the fiberscope proved to be of greater value than the telescope. In these 10 patients, the entirety of the vocal folds could not be satisfactorily visualized for telescopic stroboscopic observation because of partial obstruction by the arytenoids or supraglottic structures. In 4 of these 10 cases, telescopic examination was impossible because of hyperactive gag reflexes.

Stroboscopic evaluation data in our study were based on the information obtained during sustained phonation /i/ for both fiberscopic and telescopic

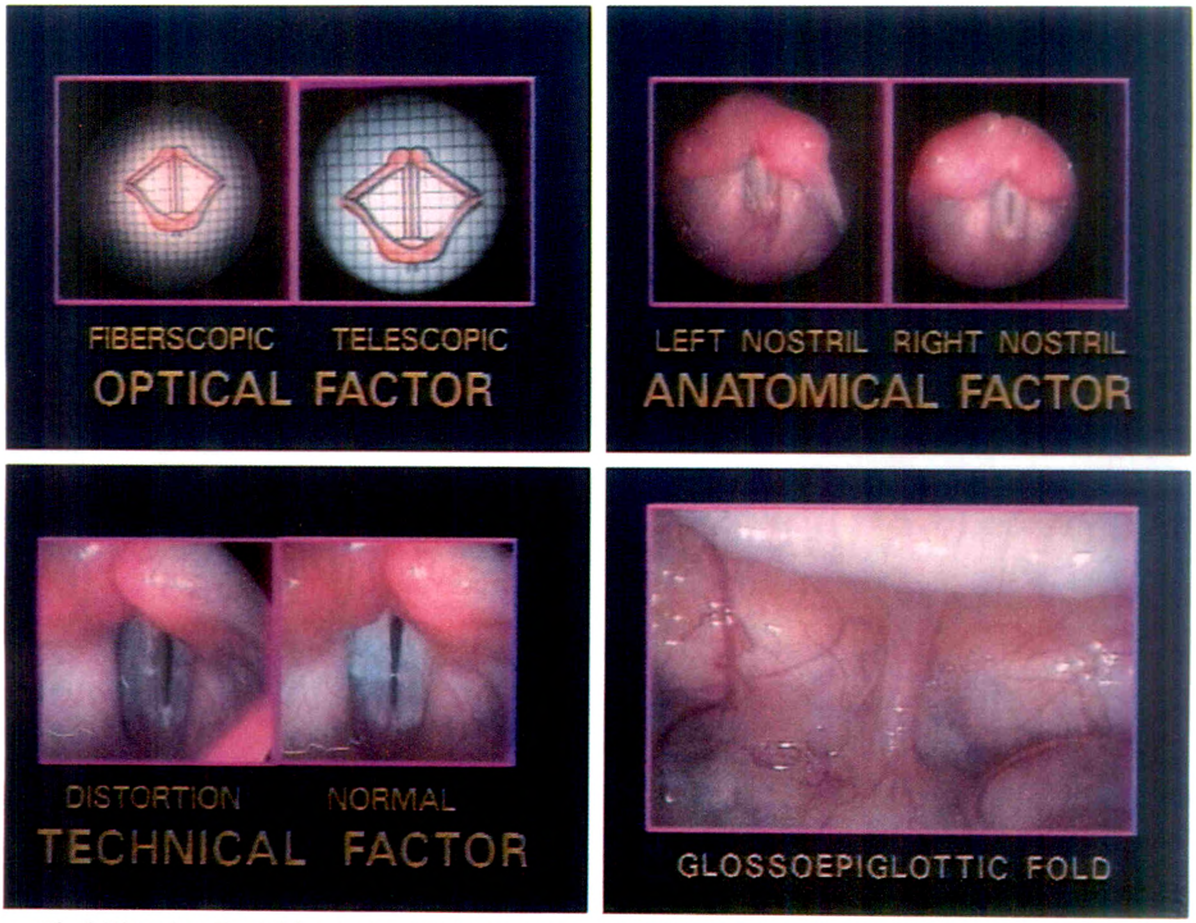

Fig 6. Distortion. Top left image shows distortion due to optical factor. Fiberscopic view shows distorted image. Note curvature of square grid at periphery. Telescopic view shows no distortion of square grid. Top right image shows distortion due to anatomic factor. Fiberscopic view through left nostril demonstrates asymmetric view of vocal folds that results from angulation of fiberscope tip secondary to left nasal septal deviation. When fiberscope is passed through opposite, right nostril, image distortion is resolved. Lower left image shows distortion due to technical factor. Telescopic view on left shows asymmetry of vocal folds resulting from passage of rigid telescope lateral to midline. When telescope is repositioned in midline (view on right), vocal folds appear symmetric. Lower right image shows that glossoepiglottic fold serves as excellent marker for midline positioning during telescopic examination. By following glossoepiglottic fold over epiglottis, vocal folds should be visualized without technical distortion.

examination. Phonation during sustained vowel /i/ provided much more useful information for both fiberscopic and telescopic SVL than that during running speech for fiberscopic SVL.

The moiré effect,[3-5] an electronic artifact that presents as an abnormal color pattern on the video monitor, was noted in eight cases (6.0%) of fiberscopic stroboscopy (Fig 7). This effect became more noticeable when the fiberscope was turned or twisted during the examination. No telescopic cases showed the moiré effect.

In several cases, the false vocal folds were noted to partially or completely obstruct the visualization of the true vocal folds, thus making stroboscopic evaluation of vocal fold vibration difficult or impossible (Fig 8). We noted that in 22 cases (16.4%) the false vocal fold obstruction was worse on fiberoptic SVL and was improved or eliminated during telescopic SVL. In 3 cases (2.2%) there was no change in the degree of obstruction by either method. In 3 cases (2.2%) false vocal fold obstruction was worse on telescopic stroboscopy.

DISCUSSION

Stroboscopic videolaryngoscopy can be performed with either the flexible fiberscope or the rigid telescope. We will discuss the advantages and disadvantages of each technique and present our recommendations for SVL.

ADVANTAGES OF FIBERSCOPIC SVL

The advantages of fiberscopic SVL include the following.

1. It is easily performed and well tolerated, even by children and by adults with a hyperactive gag reflex.

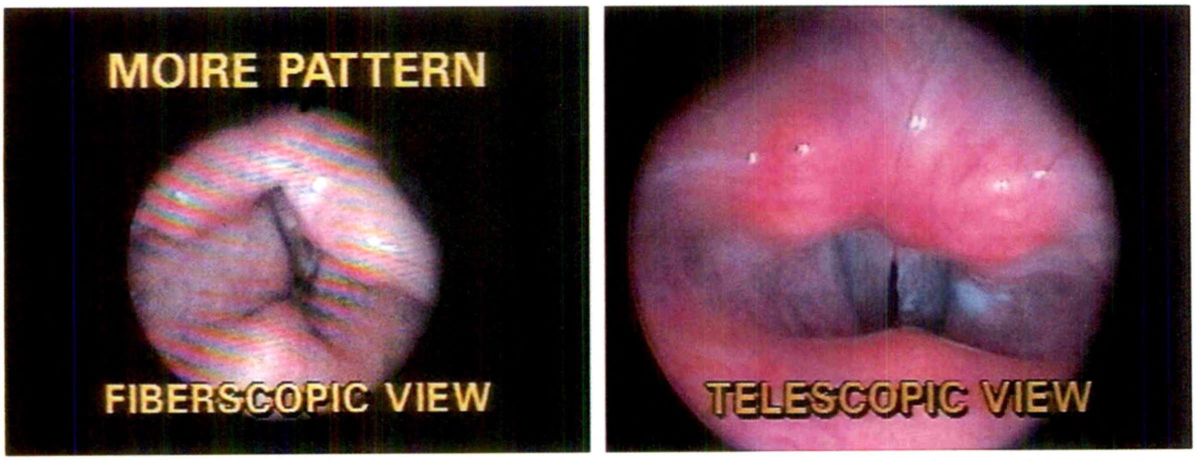

Fig 7. Moiré effect (left), electronic artifact that results in annoying colored patterns on video monitor. Note that telescopic SVL never shows moiré effect.

2. It can be done in patients with an anomalous epiglottis or obstructive supraglottic lesions.

3. When the patient is well anesthetized, the tip of the fiberscope can be advanced to a position very close to the vocal folds, affording an enlarged view of the larynx. The larger the vocal folds appear on the monitor, the better the detail and the anatomic visualization for stroboscopic analysis.

4. The patient can adopt a normal head position, and vocal fold vibrations and movements seen during fiberscopic SVL more closely simulate the movements produced during natural speech.[36]

5. The subglottic region and the ventricles can also be examined.

6. A panoramic view of the hypopharynx, the base of the tongue, and supraglottic structures can be obtained prior to or during stroboscopy, and allows observation of movements and lesions of the lateral hypopharyngeal walls.

DISADVANTAGES OF FIBERSCOPIC SVL

The disadvantages of fiberscopic SVL include the following.

1. The image on the monitor is often small, and often of rather limited resolution, making evaluation of stroboscopic parameters difficult.

2. The image may appear distorted because of optical factors.

3. The distortion may result from anatomic factors such as a septal deviation or spur. Symmetry of vocal fold vibration cannot be accurately assessed when the vocal folds are distorted.

4. A very small, early lesion of the vocal folds may not be well appreciated.

5. It is not always easy to stabilize the tip of the fiberscope during stroboscopy.

6. Disturbing moiré effects (unwanted color stripes) are peculiar to fiberscopic documentation. This can often be eliminated by turning the head of the fiberscope, although the vocal fold image may not look perfectly vertical.

7. False vocal fold constriction or obstruction, seen in some patients, will make stroboscopic evaluation of the vocal folds difficult or impossible.

8. Video documentation may not be easy because of lack of illumination.

ADVANTAGES OF TELESCOPIC SVL

The advantages of telescopic SVL include the following.

1. The telescopic images are larger and brighter, with excellent color and resolution.

2. Vocal fold vibrations and mucosal waves can be assessed more easily and accurately.

3. Early detection of invasive tumor and other small lesions is possible.

4. Little optical distortion is noted.

5. False vocal fold constriction or obstruction encountered during fiberscopic examination may improve during telescopic examination in patients.

6. Video documentation is easier and high-quality stroboscopic images can be obtained.

DISADVANTAGES OF TELESCOPIC SVL

The disadvantages of telescopic SVL include the following.

1. It is often difficult or impossible to examine children and adults with a hyperactive gag reflex and

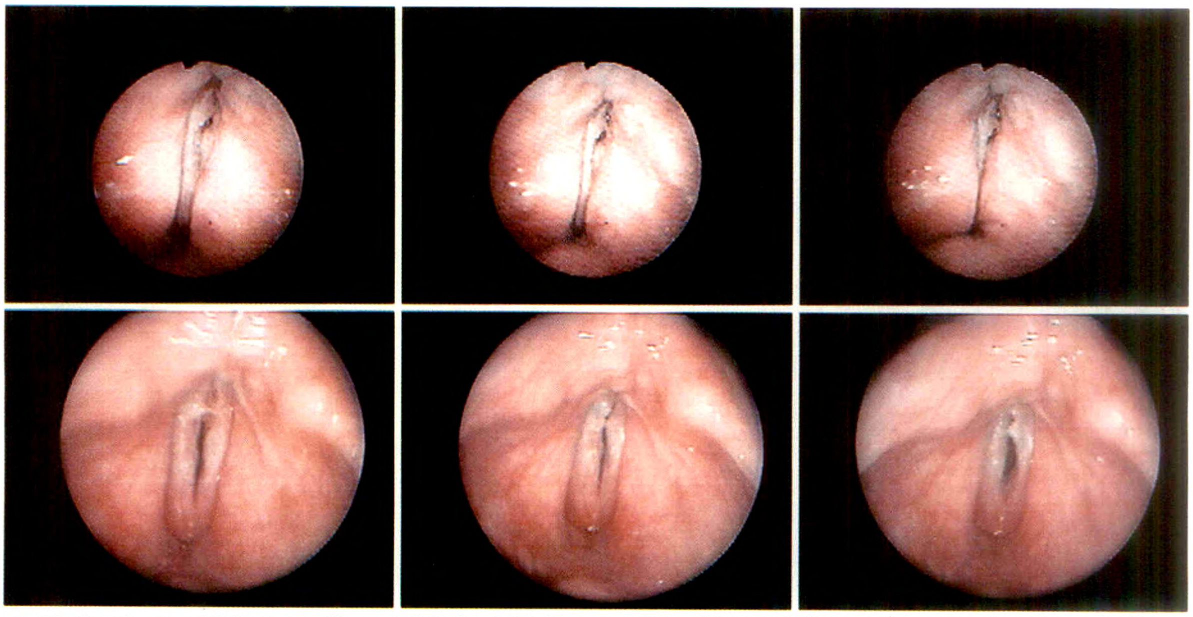

Fig 8. False vocal fold obstruction noted during SVL. Top row shows fiberscopic images demonstrating obstruction by false vocal folds at normal pitch and loudness, making stroboscopic evaluation of underlying vocal folds impossible. Bottom row shows telescopic images of same patient at same normal pitch. False vocal fold obstruction was resolved with tongue pulled out, hence making stroboscopic evaluation of vocal folds possible.

those patients with an anomalous epiglottis or large supraglottic lesions.

2. The patient has to adopt an unnatural head position that interferes with normal phonation.[23]

3. The tip of the telescope lens may become fogged from the patient's breathing, and the telescope may need to be removed for cleaning.

RECOMMENDATIONS

In order to obtain the best possible videostroboscopic images of the larynx, the authors recommend the following general considerations.

1. When the stroboscopic images are blurred, clean the lens of the fiberscope or telescope (alcohol wipes, warm water, etc).

2. Explain the procedure to the patient prior to the stroboscopic examination. Placement of a small extra television monitor in front of the patient may permit the patient to observe the procedure and to cooperate better with the examiner.

3. Always examine the vocal folds at the patient's normal, high, and low pitches. Images of high-pitch phonation will show stiffness of the vocal folds with diminished mucosal waves and amplitude, while those of low-pitch phonation will show increased mucosal waves and amplitude well (Figs 3 and 4).

4. White-balance the video camera prior to the examination, particularly when the stroboscopic image appears bluish.

5. Record stroboscopic findings on assessment forms as suggested by Bless et al,[4,5] so that systematic, consistent documentation of findings is kept for all subjects.

For fiberscopic SVL, we suggest the following.

1. Use the more patent nasal passage to minimize the extent of fiberscopic image distortion (asymmetry).

2. Use close-up fiberscopic images to obtain the largest possible image size. To achieve successful fiberscopic stroboscopic images, adequate topical anesthesia of the supraglottic area is essential.

3. Refocus fiberscopic image on the monitor before recording. This can be done with either focusing dial of the fiberscope or that of the endoscopic adapter of the video camera.

4. To improve dark fiberscopic SVL images, use an extra–light-sensitive video camera (low lux) or increase the video camera sensitivity by using the gain control switch; advance the tip of the fiberscope very close to the vocal folds; change the image size by using a zoom adapter for a micro CCD camera, or a zoom lens of a home video camera; or use a fiberscope with a larger diameter such as the Olympus ENF-L (4.4 mm).[23]

For telescopic SVL, we suggest the following.

1. Apply adequate topical anesthesia to the posterior pharyngeal wall and the base of the tongue. If the patient gags, do not give up. Reassure the patient,

apply additional topical anesthesia, and reexamine.

2. Maintain a midline position of the telescope to minimize image distortion by following the glosso-epiglottic fold.

3. Use a 70° or 60° forward oblique telescope, such as the Nagashima SFT-1, rather than a 90° telescope, for better visualization of the entire vocal folds. The authors have obtained excellent results with the 70° telescope, while Yamashita[35] recommends the 60° telescope for better visualization of the posterior larynx without obstruction by the arytenoids.

SUMMARY

Telescopic SVL provides superior images, better documentation, and more valuable clinical information compared to fiberscopic SVL. Telescopic SVL is the authors' choice for patients selected for laryngeal stroboscopy.

For those patients with hypersensitive gag reflexes and children who cannot tolerate the telescopic procedure, or for the patient whose larynx cannot be visualized because of supraglottic lesions or anatomic anomalies, fiberscopic SVL is recommended.

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FIRST CONGRESS OF EUROPEAN SKULL BASE SOCIETY

The European Skull Base Society will hold its first congress September 26-30, 1993, in Riva del Garda (Trento), Italy. For further information contact Carmelo Zappone, MD, Congress Secretary, Division of ORL, Ospedali Riuniti, Largo Barozzi 1, 24100 Bergamo, Italy; telephone 35-269578; fax 35-269460.

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PEDIATRIC SINUS ENDOSCOPY COURSE

The postgraduate Pediatric Sinus Endoscopy Course will be held June 10-12, 1993, at St Louis Children's Hospital, St Louis, Missouri. Participants should have taken a previous endoscopic sinus surgery course, and their practice should consist of a large group of pediatric patients. For further information, contact Marilyn Crawshaw at (314) 454-2138.

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RIGID BRONCHOSCOPY BALLOON CATHETER DILATION FOR BRONCHIAL STENOSIS IN INFANTS

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Stenosis of the tracheobronchial tree can be a life-threatening problem. Management options for symptomatic stenosis include serial dilation, cryotherapy, laser resection, and open surgical correction. Recently, balloon angioplasty catheters have been used to dilate stenotic airway segments. The experience in infants is limited and has for the most part utilized guide wires and fluoroscopy for balloon placement. We present two infants with symptomatic bronchial stenosis who underwent endoscopic angioplasty balloon catheter dilation. Operative technique involved catheter placement under direct vision with a rigid bronchoscope. Catheters (6F) with 8-mm-diameter balloons were used. Balloon expansion was controlled with a hand-held manometer. Both infants demonstrated significant lumen size improvement intraoperatively and marked clinical improvement postoperatively, substantiated by endoscopy and radiographs. One infant has required one repeat dilation and has subsequently been asymptomatic. The other infant has had no further respiratory problems. Our technique, using a rigid bronchoscope with direct visualization of catheter placement, obviates the need for guide wires and C-arm fluoroscopy as previously described. Endoscopic placement enables direct visualization of balloon position, and fine adjustments are possible if further dilation is necessary. Rigid bronchoscopic balloon catheter dilation can be a successful technique for bronchial stenosis and should be considered prior to attempting more invasive surgical correction.

KEY WORDS — balloon catheter, bronchial stenosis, dilation, rigid bronchoscopy.

INTRODUCTION

Tracheobronchial stenosis in infants is a difficult problem with significant morbidity and mortality. Techniques for managing these children have included successive dilation,[1] cryotherapy,[2] laser photoresection,[3-5] and open surgical correction.[6] Recently, several reports have described successful management of stenotic airway segments with angioplasty balloon catheters.[7-12] All but one of the previous reports in infants have shown use of guide wires and fluoroscopic catheter placement. Our purpose in presenting this series is severalfold: 1) to reaffirm the clinical potential of this technique, 2) to discuss the advantage of balloon catheter placement and expansion under direct visualization over guide wires and fluoroscopy, 3) to present our long-term success in managing two infants with bronchial stenosis using only angioplasty catheters, and 4) to introduce this technique to the otolaryngology–head and neck surgery literature.

CASE REPORTS

Case 1. A 6-month-old boy presented for further evaluation of respiratory distress and recurrent pneumonia. This child was the product of a full-term gestation that came to cesarean section because of cephalopelvic disproportion and 48 hours of premature rupture of membranes. The child was intubated at birth for respiratory distress and maintained on a ventilator for 10 days with group B streptococcal pneumonia. At 14 days of age, the patient was discharged with only occasional wheezing that was managed with bronchodilators as needed. The patient did well until the age of 5 months, when he developed a fever and increasing respiratory distress. He was admitted and intubated for airway management. *Mycoplasma* pneumonia was diagnosed and erythromycin ethylsuccinate was started. Flexible bronchoscopy demonstrated right main stem bronchial edema. Intravenous corticosteroids were initiated, followed by marked clinical improvement, extubation, and eventual discharge. The patient continued to be symptomatic. Repeat chest radiography (CXR) demonstrated persistent right lung atelectasis. The patient was then transferred to our facility for further evaluation. On admission, CXR demonstrated right lung atelectasis, left lung hyperlucency, and mediastinal shift to the right (Fig 1A). Magnetic resonance imaging (MRI) ruled out extrinsic compression and showed narrowing of the right main stem bronchus, with normal caliber of the distal segments. Because of

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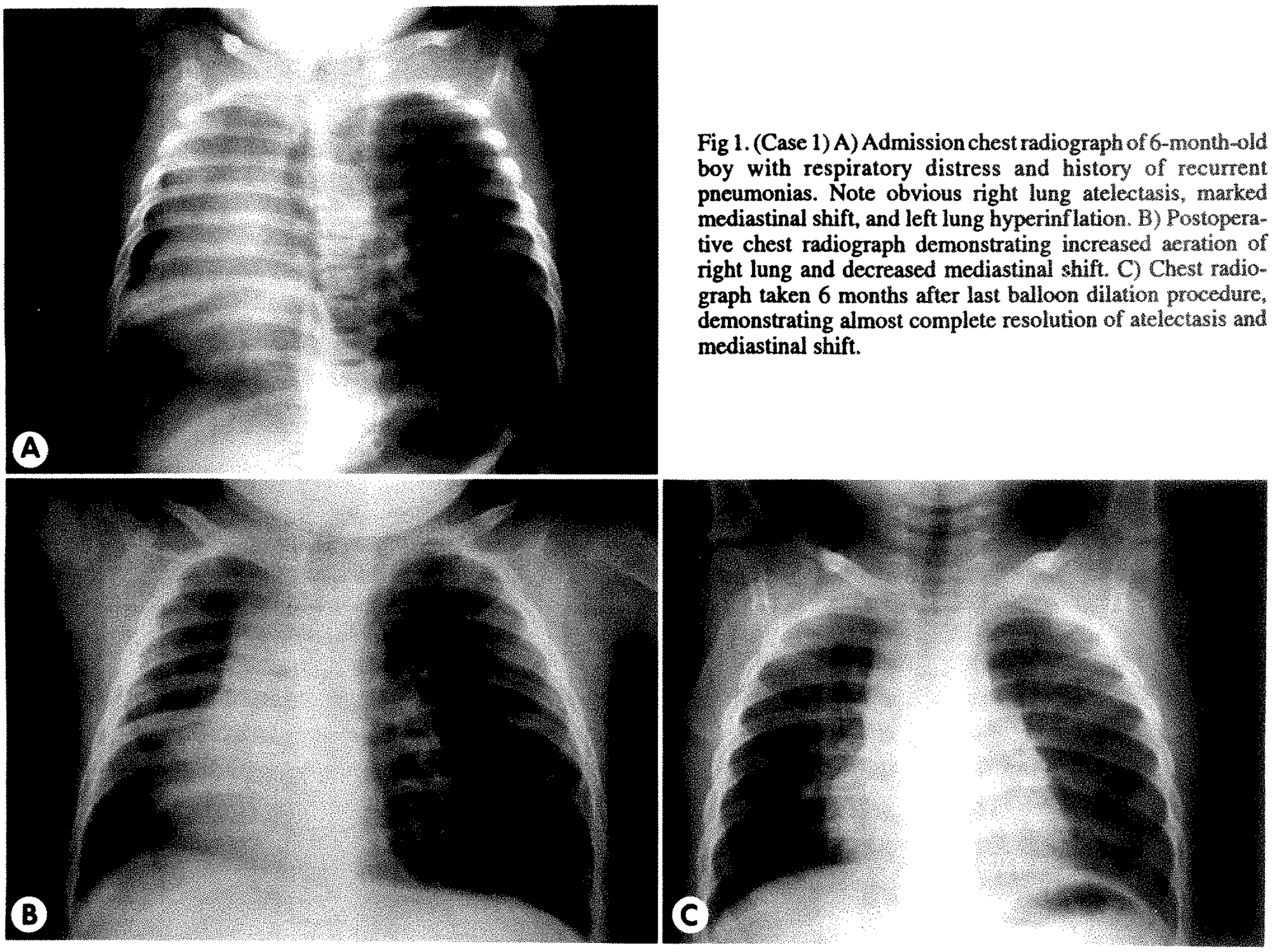

Fig 1. (Case 1) A) Admission chest radiograph of 6-month-old boy with respiratory distress and history of recurrent pneumonias. Note obvious right lung atelectasis, marked mediastinal shift, and left lung hyperinflation. B) Postoperative chest radiograph demonstrating increased aeration of right lung and decreased mediastinal shift. C) Chest radiograph taken 6 months after last balloon dilation procedure, demonstrating almost complete resolution of atelectasis and mediastinal shift.

continued symptoms, the patient was taken to the operating room, where two balloon dilations were performed on a firm concentric lesion, showing obvious lumen size improvement (Fig 2). Postoperatively, the patient showed marked clinical improvement, and CXR demonstrated increased aeration of the right lung (Fig 1B). After discharge, repeat flexible bronchoscopy showed an improved right bronchial airway but evidence of a persistent shelf. Four weeks after his procedure, the patient was taken back to the operating room, where he was redilated. Repeat flexible bronchoscopy and CXR have demonstrated almost complete resolution of stenosis and atelectasis (Fig 1C). This child, now 30 months from his last dilation procedure, remains asymptomatic.

Case 2. A full-term male product of an uncomplicated pregnancy presented at 5 months of age for evaluation of persistent cough and wheezing that began 2 weeks after birth. Nine days prior to referral to our institution, a diagnosis of reactive airway disease had been made and the patient had been started on anhydrous theophylline and corticosteroids. On admission, the patient had decreased breath sounds in the left side of the chest, and CXR showed left lung hyperaeration (Fig 3A). Flexible bronchoscopy demonstrated marked narrowing of the left main stem bronchus. An MRI scan ruled out extrinsic compression of the airway. The patient was then taken to the operating room, where his left main stem bronchus was dilated with a balloon angioplasty catheter. The stenotic segment was firm, approximately 2 cm in length, and found just below the carina. Three successive dilations were done with advancement of the catheter after each inflation. A 3.5-mm rigid bronchoscope was easily passed below the stenotic area after the third dilation. The patient's respiratory condition was significantly improved following this procedure. Postoperative CXR showed decreased hyperinflation of the left lung (Fig 3B). The patient remains asymptomatic 22 months from the above dilation procedure.

TECHNIQUE

Anesthesia was obtained using halothane with 100% oxygen and topical laryngotracheal 4% lidocaine hydrochloride. Intraoperative monitoring included continuous pulse oximetry and blood pressure measurements. A 3.5-mm Storz pediatric rigid bronchoscope was used for both patients. Gruentzig balloon angioplasty catheters (6F) with an 8-mm balloon (Cook, Inc, Bloomington, Ind) were used.

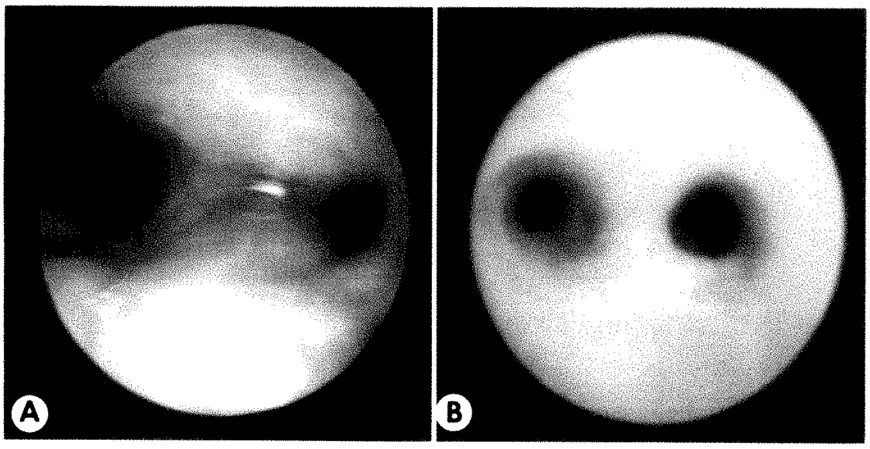

Fig 2. (Case 1) Intraoperative photograph taken just above carina. Note A) obvious right main stem stenosis and B) post-balloon dilation improvement.

Catheters were passed through the instrument side port of the bronchoscope. Balloon placement and inflation were both monitored by direct visualization. Balloon pressures were regulated by an interposed hand-held manometer (Fig 4). Inflations were maintained from 10 to 30 seconds at 6 atmospheres of pressure. Airway adequacy was assessed by partially withdrawing the catheter. Fine catheter adjustments for further dilation were easily accomplished by direct visualization. Repeat dilations were performed on both patients during the initial procedure until obvious airway improvement was obtained. Intravenous Decadron (0.5 to 1 mg/kg) was administered at the end of each procedure.

DISCUSSION

Multiple techniques have been employed to correct tracheobronchial stenosis in infants. Management options range from watchful waiting to sleeve resection of stenotic segments. Although open surgical techniques have been considered definitive management for significant stenosis, less invasive procedures have demonstrated good results in select individuals. The simplest form of treatment is to successively dilate stenotic airway segments under anesthesia. This method has been advocated for some stenoses and can be easily performed with little technical expertise.[1] Another minimally invasive technique utilizes cryotherapy.[2] This technique involves the use of a 3-mm-diameter nitrous oxide cryoprobe that is applied to stenotic lesions through a rigid bronchoscope. Frozen fibrogranulation tissue is then removed with cup forceps. Select subglottic, tracheal, and bronchial lesions have been treated successfully with this method. Morbidity and recurrence are infrequent, and repeat applications are recommended as needed. Laser photoresection is another method for correcting stenotic airway segments. Neodymium: yttrium-aluminum-garnet (Nd-YAG) and argon lasers have both been used with good success in both children and adults.[3-5] The Nd-YAG laser is less useful in pediatric airways because of the large size of its fiberoptic cables. Carbon dioxide lasers are also of limited use in pediatric airways because of the inability to use this laser through a fiberoptic cable. A recent report by Azizkhan et al[3] describes manage-

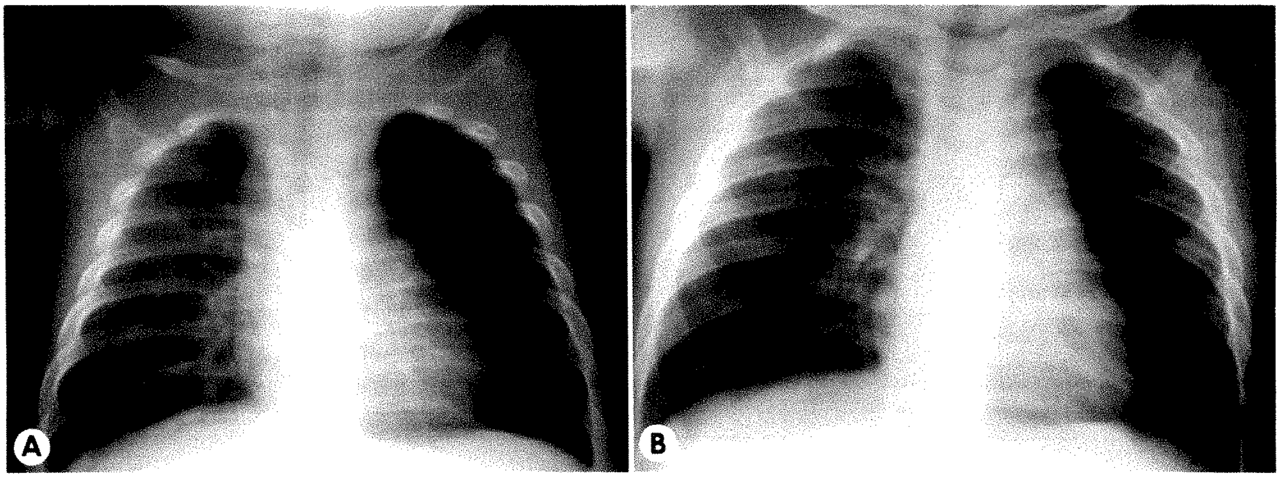

Fig 3. (Case 2) A) Admission chest radiograph of 5-month-old boy with respiratory distress and decreased breath sounds from left side of chest. Note left lung hyperaeration. B) Chest radiograph taken 2 months after balloon dilation of left main stem bronchial stenosis demonstrating almost complete resolution of left-sided hyperlucency.

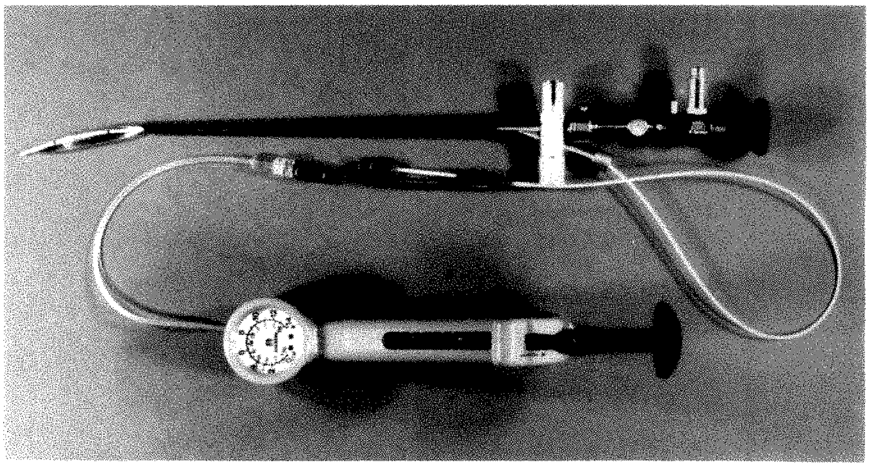

Fig 4. Balloon angioplasty catheter passed through side port of rigid bronchoscope with manometer attached.

ment of bronchial stenoses in infants with the use of an argon laser. Several of these children also had concomitant balloon dilation. Seven of the eight infants in this series have had satisfactory results, but the effects of balloon dilation could not be assessed. Although cryotherapy and laser photoresection are efficacious therapies for managing infantile airway stenosis, sophisticated equipment and technical expertise are necessary to implement these treatments.

Balloon angioplasty catheter dilation offers an alternate mode of therapy that does not require expensive equipment or additional expertise of an experienced endoscopist. Since this technique was introduced in 1984 by Cohen et al,[7] multiple case reports have attested to its clinical applicability.[7-12] Both acquired and congenital lesions have been managed successfully. Techniques for the most part have utilized guide wire placement of catheters with balloon positioning determined by C-arm fluoroscopy. Our technique demonstrates the advantage of catheter placement and expansion under direct visualization through the bronchoscope. This method allows accurate catheter positioning and continuous visual monitoring during inflation. After deflating the balloon and partially withdrawing the catheter, the stenosis can be reassessed and fine catheter position adjustments made for subsequent inflations. A good example of this is the child in our second case report. After the first dilation, a deeper stenosis was encountered and deeper placement of the catheter was required for adequate correction. Direct visualization allowed proper catheter positioning that may not have been possible with fluoroscopy. Our technique also circumvents the potential risks of irradiation and the use of guide wires in the airway.

Attention should be drawn to a recent report of Hebra et al.[12] This series describes the management of 37 children (average age 5 years) with airway stenosis using balloon catheter dilation. Their technique, as ours, utilized direct visualization of catheter placement and inflation through a rigid bronchoscope. In this series, only two patients had bronchial stenoses, both of which were acquired. No details are given as to patient age or chronicity of symptoms. Both of these patients had immediate improvement, but had deteriorated by a 2-month follow-up. No further mention of treatment outcomes is made for these two patients. Overall, Hebra et al report excellent short-term results in 90% of their patients, but only 54% have continued to demonstrate improvement (minimum of 2 months for long-term follow-up). Chronic well-formed or calcified strictures and glottic strictures are cited as areas of failure. In our series, both patients were treated at a very young age, probably prior to significant stricture maturation. Strictures treated after scar organization and calcification would be expected to respond less well to dilation attempts. The mechanism for persistent dilation of congenital bronchial lesions following balloon catheter dilation is unknown, but may be related to early diagnosis and treatment. Currently, both of our patients have remained asymptomatic for 22- and 30-month intervals following their last dilation procedure. Although the long-term efficacy of this treatment modality has not been fully demonstrated, our preliminary results seem promising and suggest the need for further investigation.

CONCLUSIONS

1. The use of balloon angioplasty catheters to dilate stenotic airway segments has proven to be efficacious for select lesions and can be easily performed by experienced endoscopists.
2. Catheter placement and inflation under direct visualization allows for accurate airway dilation without unnecessary surgical risks.
3. Early lesion identification and treatment may be important in achieving long-term results with this technique.

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INTERNATIONAL CONFERENCE & COURSE ON STEREOTACTIC RADIOTHERAPY/RADIOSURGERY

The International Conference & Course on Stereotactic Radiotherapy/Radiosurgery will be held May 6-8, 1993, at Free University Hospital, Amsterdam, the Netherlands. For further information, contact Congress Secretariat (Ms A. Sol, Ms G. Luysterburg), VU-Ziekenhuis, Postbus 7057, 1007 MB Amsterdam, the Netherlands; phone 31-20-548 6163 or 548 6164; fax 31-20-548 6160 or 548 6101.

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EIGHTEENTH DANIEL C. BAKER, JR, MEMORIAL LECTURE
ART AND SCIENCE OF LARYNGEAL PHOTOGRAPHY

BRUCE BENJAMIN, FRACS, FAAP

SYDNEY, AUSTRALIA

Photography of the pharynx, larynx, and trachea has exercised the ingenuity of laryngologists and photographers for 100 years. There have been many successful methods. The most reliable and versatile modern system uses a 35-mm single frame, single lens reflex camera with Hopkins telescopes and a synchronized, automatic exposure, computer-controlled, remote electronic flash generator. The technique described, which has been used by the author for many years, not only allows excellent visualization and reliable documentation, but yields consistently reproducible photographs under all conditions.

KEY WORDS — **documentation, larynx, photography.**

Laryngeal photography has fascinated physicians since the first successful attempt over 100 years ago by French[1] of New York using sunlight from a head mirror, a laryngeal mirror, and a primitive photographic device. In the 1940s and 1950s Holinger[2] used the specially constructed Holinger-Brubaker endoscopic camera,[3] which by modern standards was heavy and cumbersome, but some of the results have not been bettered even with present-day highly sophisticated technology. A number of textbooks and atlases[4-8] feature the pictorial results of various photographic techniques, but they do not give details of the techniques.

TECHNIQUES

Photography of the laryngopharynx has been achieved in many ways, including use of a laryngeal mirror, 70° or 90° rigid telescopes, and flexible fiberoptic instruments, or by direct laryngoscopy, sometimes making use of the optics of the operating microscope. Usually, the more expensive the equipment, the more reliable it is and the better the image. Some of the techniques documented have been indirect mirror laryngoscopy,[9] indirect laryngoscopy using an angled rigid rod lens telescope[10,11] in the office, flexible fiberoptic laryngoscopy,[11,12] and direct laryngoscopy. Direct laryngoscopy photographic techniques include use of the Holinger-Brubaker camera,[3] the single lens reflex (SLR) camera with a close-up lens (either a telephoto lens [100 mm] or a macrolens [50 mm][12]), the SLR camera and a close-up lens with a ring flash,[12] telescopic photography using a 0° or 30° telescope for both illumination and flash illumination during direct laryngoscopy in the operating room,[10,13,14] photography through the microscope (photography through a beam splitter,[4,13,15] a photo adaptor attached to the eyepiece,[16] and the "macrolens technique"[17]), and television monitor "instant" video prints.[15,18]

While the flexible fiberoptic instruments are versatile and have the great advantage of passing around corners, neither the visual nor the photographic image is as good as that obtained with the Hopkins rigid fiberoptic telescopes.

PROBLEMS AND DIFFICULTIES

Some of the problems encountered by dissatisfied and frustrated photographers include blurring or difficulty with focusing, improper centering, restricted depth of focus, inadequate lighting, difficulty with exposure of the pathologic anatomy, lack of clarity of the image, variability in color rendition, inability to obtain consistent conditions for photography, the need for more than one operator, inconvenience and time consumption during an operation, acquisition of only a small image, the need for a tripod, and, last, the unpredictability of success. The photographic technique should not be so elaborate or complicated that it is difficult to use for an endoscopist who is not familiar with photography.

STATE-OF-THE-ART TECHNIQUE

The technique to be described has been used by the author with various modifications and improvements for many years; it allows excellent visualization and reliable documentation. It depends on the principle of housing the source of both the lighting for routine

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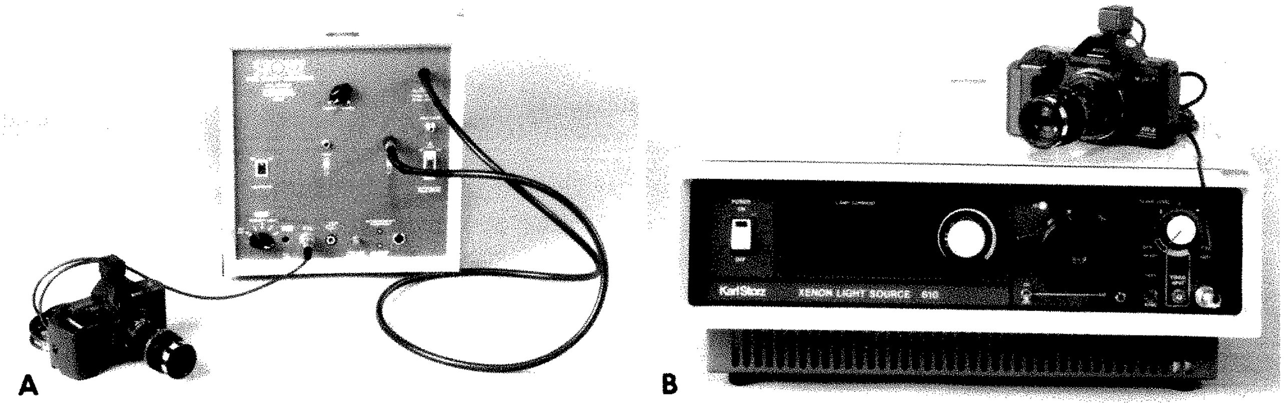

Fig 1. A) Model 600 through-the-lens computer flash unit and 35-mm camera (Karl Storz GmbH & Co, Tuttlingen, Germany). B) Model 610 xenon light source for photography and television (Karl Storz Endoscopy-America, Inc, Culver City, Calif).

examination and the momentary brilliant light for photographic exposure in the same large photographic lighting unit. A remote light source provides both continuous light for visualization and either electronic flash (Fig 1) or pulsed xenon light that is transmitted by either a fiberglass light-conducting cable or a liquid-filled light-conducting cable to a Hopkins rigid rod lens telescope attached to a special zoom lens on an SLR camera (Fig 2). Hopkins[19] of Reading University invented a rigid rod system made of tubes of glass with thin air lenses, thus creating an increase in light transmission compared to the conventional telescope with small glass lenses. All glass surfaces are multicoated, and the telescope achieves a viewing angle of 70° — equivalent to a 28-mm lens on a 35-mm camera.[20]

With this system photographic documentation of the laryngopharynx, nasal cavities, nasopharynx, and tympanic membranes can be undertaken in the office. During endoscopy in the operating room the technique can be applied not only to all areas of the larynx, but to the tracheobronchial tree, esophagus, and paranasal sinuses. It has a success rate close to 100% in both adults and children and is without question the most reliable and simple technique. It is versatile and easy to use, and the image quality and color of 35-mm transparencies cannot be bettered. Any area accessible to a telescope can be readily and reliably photographed, so routine documentation is now a practical reality.

Details of photography of the larynx and trachea will be described under the headings Equipment, Anesthesia, and Photographic Technique.

EQUIPMENT

Light Source. There are many light sources (eg, halogen, quartz iodine, xenon), and some have been adapted for photography. The illumination from a xenon light source can be easily boosted when a photograph is taken, but the best photographic lighting is electronic flash. Small sealed flash tubes attached to the telescope were used some years ago, but have been replaced by the larger computer flash units. The latest and most advanced model 600 light box (Fig 1) provides both continuous bright halogen light for viewing or use with a video camera and electronic flash for photography. The automatic light metering is provided by an SLR camera body (or more recently by a meter actually in the zoom lens itself).

There is an audible signal when the flash is fully charged and an automatic reminder of three audible "beeps" after the photograph has been taken to indicate when photographic conditions have been optimal and the exposure has been successful. If the photographic field is too far distant and the light intensity cannot illuminate the area adequately, the audio indicator remains silent. The unit has a 250-W cold light halogen lamp with continuous light adjust-

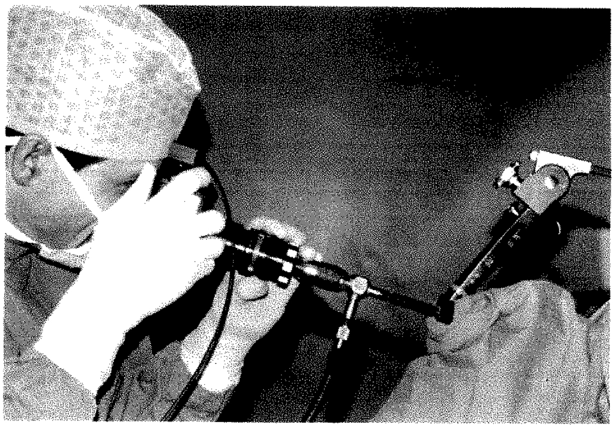

Fig 2. Laryngeal photography using rigid telescope during suspension laryngoscopy under general anesthesia. Left hand sets zoom lens and adjusts focus.

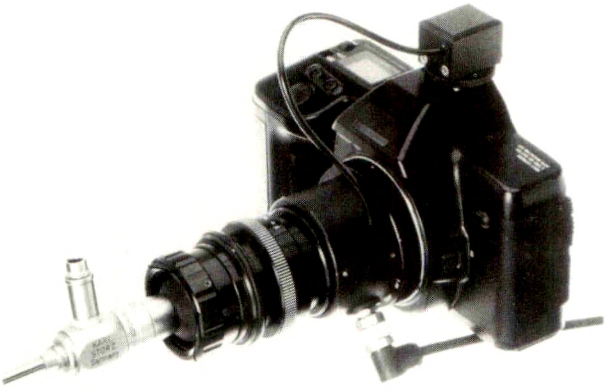

Fig 3. Newest camera for endoscopic photography, with automatic electronic light meter now integrated into zoom lens.

able in four steps of intensity for routine examination, and there is a built-in spare lamp that can be switched on should the first lamp fail. A choice of two outlets for flash is available. The unit is used with automatic through-the-lens (TTL) computerized flash metering for precise and accurate exposure. There is an antifog airpump to avoid fogging of the telescope objective, but a simple and effective alternative is application of an antifog solution immediately before the telescope is used.

This sophisticated system, although expensive, gives uniform picture quality and optimal exposure; its operation has been found reliable over years of regular use.

Camera. An SLR camera (Fig 2) with automatic light metering is used with the TTL computer flash unit for endoscopic still photography. The function controls on some camera bodies have a choice of center-weighted "spot" metering or "peripheral" metering to measure light reflected from the film. For laryngeal photography the difference is seldom important. The camera must have a modified plain, clear viewing and focusing screen to admit sufficient light through the telescopes for a brighter and better-defined image and accurate focusing. An electric synchronization cable connects the hot shoe on the top of the camera to the multipin plug on the front of the lighting unit. The camera body has built-in motor drive for film advance, allowing photography to be performed every few seconds (as soon as the capacitor has charged the flash unit), and there is an optional data display camera back (for imprinting figures and letters on the film) interchangeable with the standard camera back.

Lens. The special zoom lens with a focal length variable from 70 to 140 mm attaches to the front of the camera body, and there is a spring-loaded adaptor with quick-fitting attachment on the front of the lens to lock the Hopkins telescope securely into place. This well-known zoom lens has recently been improved by addition of an integrated electronic light meter for automatic exposure metering within the lens itself (Fig 3), thus having the advantage that it can be used with any SLR camera body.

The size of the image on the film is determined by the focal length of the lens together with the diameter and angle of view of the telescope (Fig 4). Choice of a longer focal length gives a larger image that almost fills the screen, producing a partly circular, partly rectangular image. Final focusing is achieved by turning an easy-to-use focusing ring on the lens.

As an alternative to a zoom lens a fixed focus conventional 80-mm or 100-mm "standard" lens with a suitable mount adaptor can be used, but there

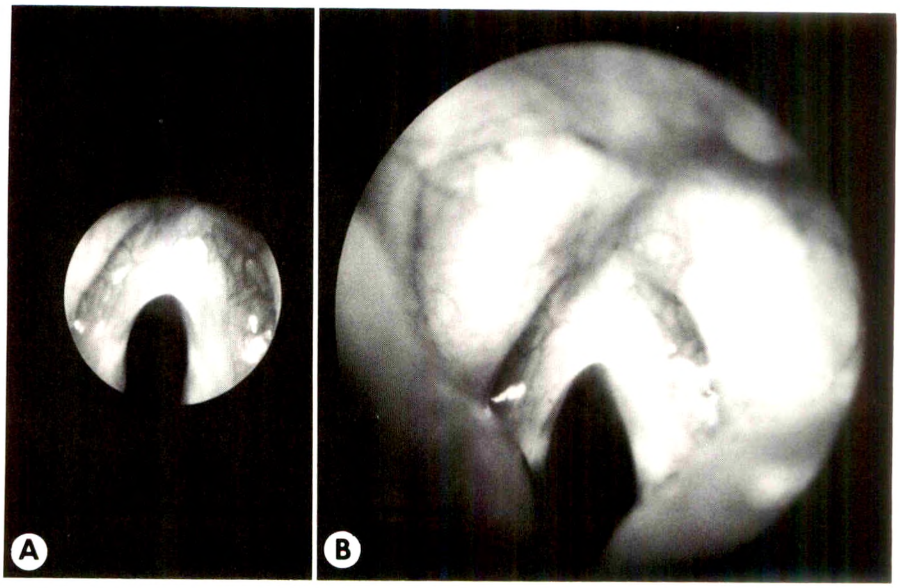

Fig 4. A) Taken with 1.9-mm-diameter telescope. B) With same focal length, taken with 5.8-mm telescope.

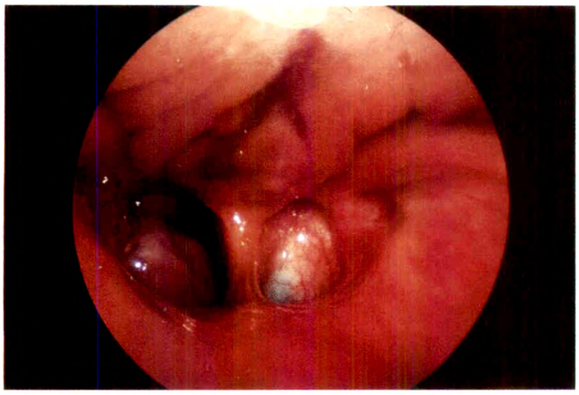

Fig 5. Nasopharynx with 120° telescope placed retropalatally, showing unilateral posterior congenital choanal atresia.

is no choice of image size, the diameter of the image depending on the particular telescope used.

Film. Kodak daylight film has a fine grain and good color tone reproduction. Ektachrome ISO200 and Kodachrome ISO200 (or any comparable film) are the standard films for taking color transparencies. Ektachrome ISO400 can be used if faster film is required — for instance, wide shots from a distance in the laryngopharynx or for photography of the nasopharynx with a 120° telescope (Fig 5).

Black-and-white film of suitable speed gives excellent results. Nevertheless, 35-mm color film is used almost exclusively, as the transparencies can be copied, enlarged, and made into prints in color or black and white.

Telescopes. Rigid Karl Storz (or similar) Hopkins rod lens endoscopic telescopes are used. Telescopes with the circular objective viewing rod lens surrounded on one side by light-carrying fibers in a crescentic shape are satisfactory, but the new Hopkins II telescopes whose circular viewing rod lens is centrally placed and surrounded by three symmetrically placed light-carrying segments provide even illumination and almost unlimited photographic capabilities. The 0°, 10-mm-diameter, 20-cm straight-forward telescope (Karl Storz 8701AG) is recommended as the standard for documentation at direct laryngoscopy. The 0° 5.8-mm-diameter 20-cm telescope (8700A) can be routinely used for children and adults and also gives good photographs. Angled telescopes are used for photography of the laryngeal ventricle, posterior glottic space, and anterior subglottis (8701BG 30°, 10 mm diameter, and 8700B 30°, 5.8 mm diameter, are recommended). For the tracheobronchial tree the Hopkins II telescopes 27005A (0°, 4.0 mm, 30-cm length) and 27005B (30°, 4 mm, 30-cm length) are recommended. The new telescope 26006A (0°, 5 mm, 30-cm length) gives excellent results in the trachea and esophagus in both adults and children.

Telescopes by other manufacturers can be used, but the image quality and clarity and the range of sizes of the Karl Storz telescopes for photography and television documentation are excellent. They have a predictable standard brightness (except with very fine telescopes in which light transmission is limited) and uniformity from one size to the other.

Laryngoscopes. There are many designs of laryngoscopes, and each has its advantages and disadvantages for photographic use. Personal preference will determine the selection for each patient, depending on the difficulty of insertion according to the prominence of the teeth, size of the tongue, pharyngeal anatomy, neck extension, and the site and size of the laryngeal lesion. Broadly, there are three types of laryngoscope: hand-held, suspension, and special-purpose.

Hand-held laryngoscopes for diagnostic examination include instruments designed by Jackson and by Holinger, the Storz side-slotted pediatric set of four, and the Parsons pediatric set of three. These instruments can be used in front of or behind the epiglottis. Some can be suspended, some have design features to

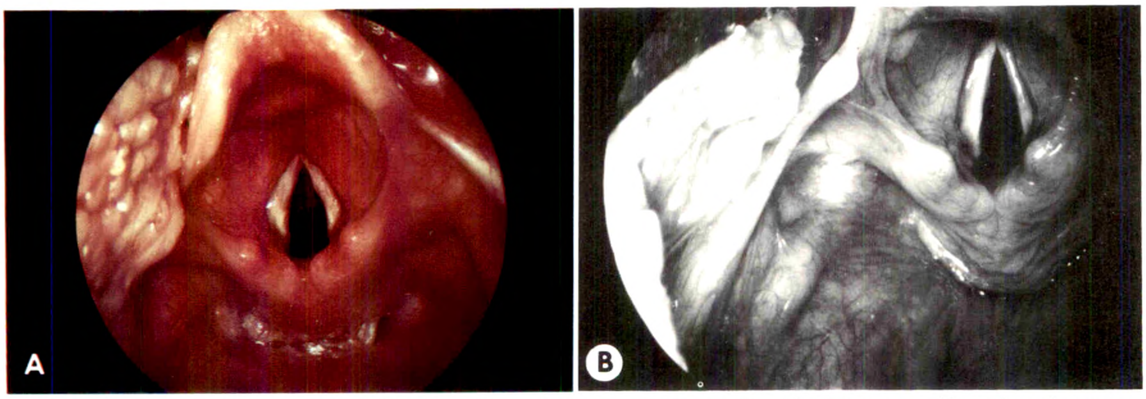

Fig 6. Lindholm laryngoscope. A) Wide view of laryngopharynx. B) By angling 0° telescope, pyriform fossa is seen, as well as larynx.

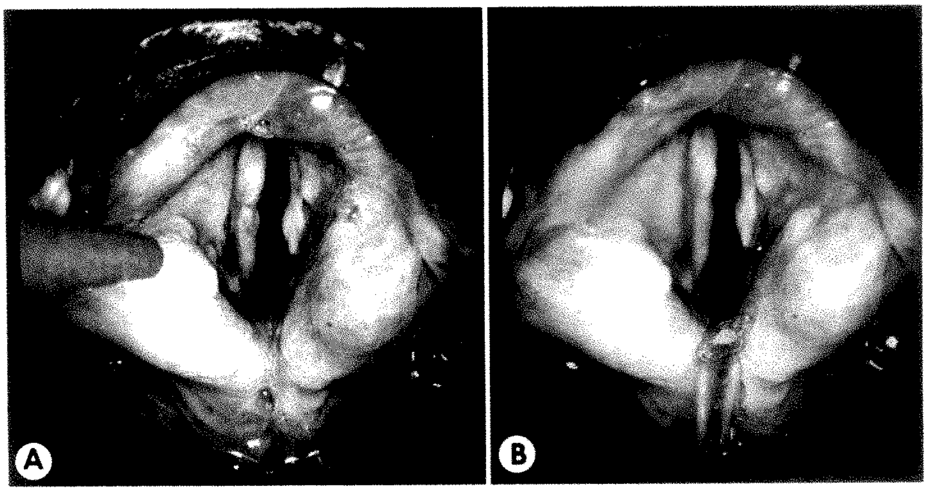

Fig 7. Jet ventilation anesthesia allows good photography. A) Proximal jet cannula (Karl Storz) inside laryngoscope. Metal cannula is slightly malleable, to direct jet into open glottic space for maximum ventilation. B) Normal glottis seen with Benjet anesthesia tube in posterior glottic space. Tube can be displaced into anterior commissure by laryngoscope for examination or operation in posterior glottic space.

assist visualization of the anterior commissure, some are slotted, some have slides, some have proximal lighting, some have distal lighting, and some have side channels either outside or inside the lumen for insufflation of anesthetic gases.

Suspension laryngoscopes free both hands for microlaryngeal or laser surgery. Commonly used laryngoscopes include the Jako, the Dedo, the Nagashima, the Lindholm, the Kleinsasser set of five, and the Benjamin pediatric. The Lindholm is ideal for photography. Placed in the vallecula, in front of the epiglottis, there is a panoramic view of the laryngopharynx (Fig 6A), not only of the vocal cords, but also of the epiglottis, aryepiglottic folds, and pyriform fossae (Fig 6B). The Benjamin slimline binocular microlaryngoscope and subglottiscope is sufficiently wide for binocular viewing using the microscope, yet narrow enough to allow examination of the larynx when other, larger instruments have failed. It is essential for adult patients in whom the larynx is difficult or impossible to visualize and photograph with standard instruments, and it gives excellent exposure of the subglottic region.

The recently released Benjamin-Lindholm laryngoscope for infants gives a remarkably wide exposure of the larynx and pharynx and is easily suspended so that telescopes can be used to precisely examine and photograph not only the larynx, but also the tracheobronchial tree.

Special-purpose laryngoscopes have special design features and include the Holinger anterior commissure laryngoscope, the Benjamin slimline laryngoscope, the distending operating laryngoscopes (eg, Weerda), and the Kantor-Berci video laryngoscope. The Kantor-Berci video microlaryngoscope is designed for documentation and for use with a video camera so that microsurgery can be performed by viewing the television monitor. It is claimed that the system substitutes for the conventional binocular operating microscope. It has disadvantages[15]: it is difficult to insert in some patients, it exposes only the glottic level, and the telescope and smoke evacuator cannulae can interfere with the passage and manipulation of instruments. However, the principle of a "fixed" unchangeable field is good for documentation, and a similar system adapted for use in other laryngoscopes would assist photography.

Bronchoscopes. The trachea, carina, and main bronchi are most conveniently examined in detail and photographed, not necessarily using a bronchoscope, but by means of a longer telescope passed through the glottic opening with the larynx in suspension while general anesthesia continues.

Tracheobronchoscopy can be performed using a ventilating bronchoscope to maintain anesthesia through the open tube while it is in the tracheobronchial tree. A bronchoscope is necessary for removal of a foreign body, for efficient suction of thick, troublesome secretions, to pass through a collapsed segment, and, sometimes, to pass into a main bronchus so that the segmental and subsegmental openings can

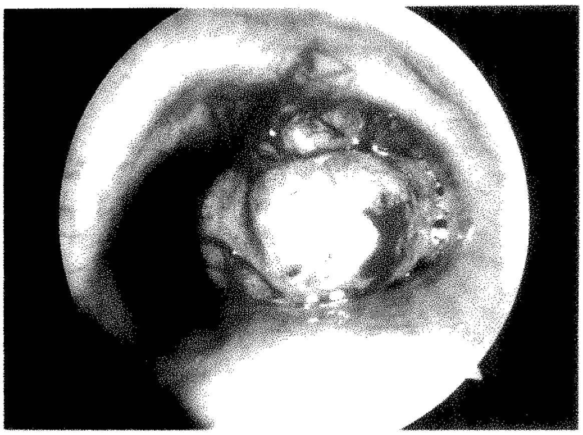

Fig 8. Ectopic salivary gland tumor (photographed with 30-cm-long, 5-mm-diameter 0° telescope) in lower trachea, almost totally obstructing right main bronchus.

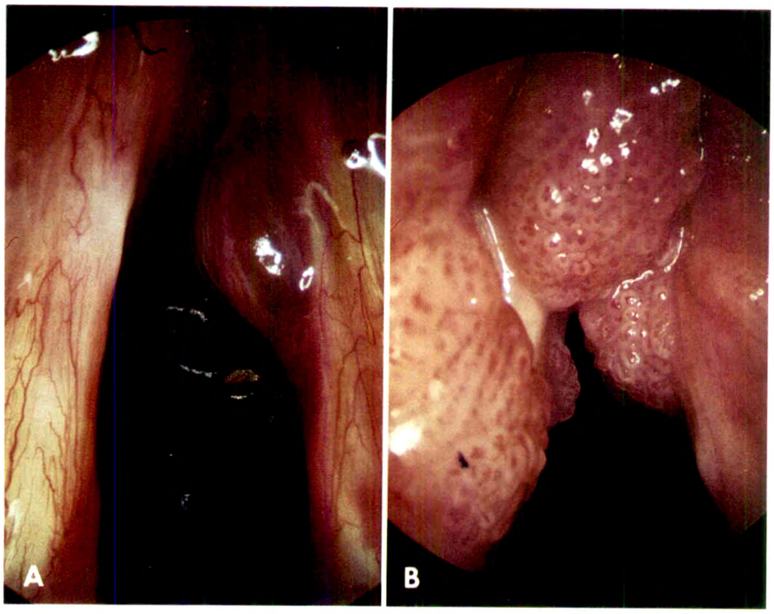

Fig 9. Close-up photography. A) Smooth polyp. B) Irregular mass of papillomas.

be examined and photographed with the 30° or 70° telescope passed through the bronchoscope itself.

ANESTHESIA

The anesthetist and the surgeon must cooperate closely to share access to the laryngeal airway — sometimes a narrow, partly obstructed, compromised airway. For photography it is vital to work with an anesthesiologist who is patient.

In the operating room, under general anesthesia, the patient lies in the supine position on a regular operating table. There is no need for a head rest or for

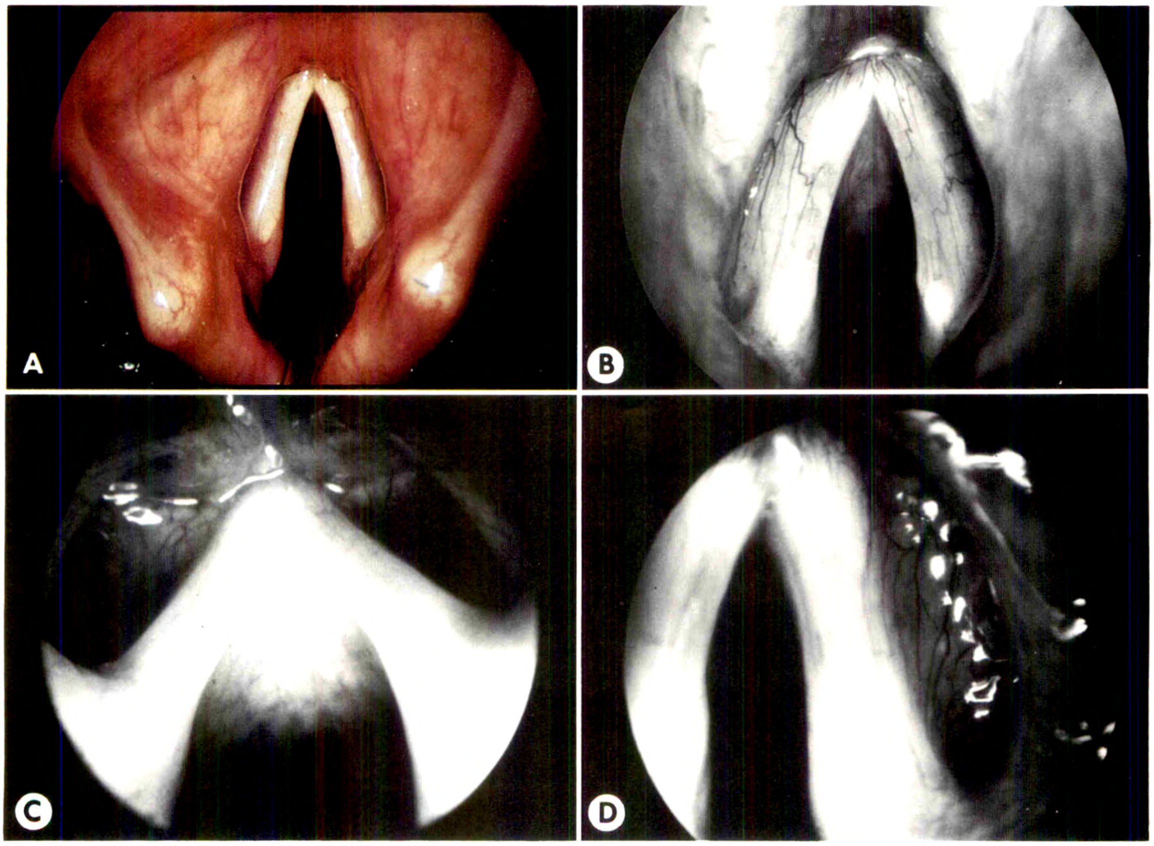

Fig 10. Normal glottis. A) With Benjet tube in posterior glottic space. B) With 30° forward-viewing telescope, showing anterior commissure of both true vocal cords and false vocal cords and "hidden" area between them. C) Same area as in B, but with 70° telescope, showing anterior subcommissure and anterior part of ventricles. D) Normal ventricle seen with 30° telescope angled to right.

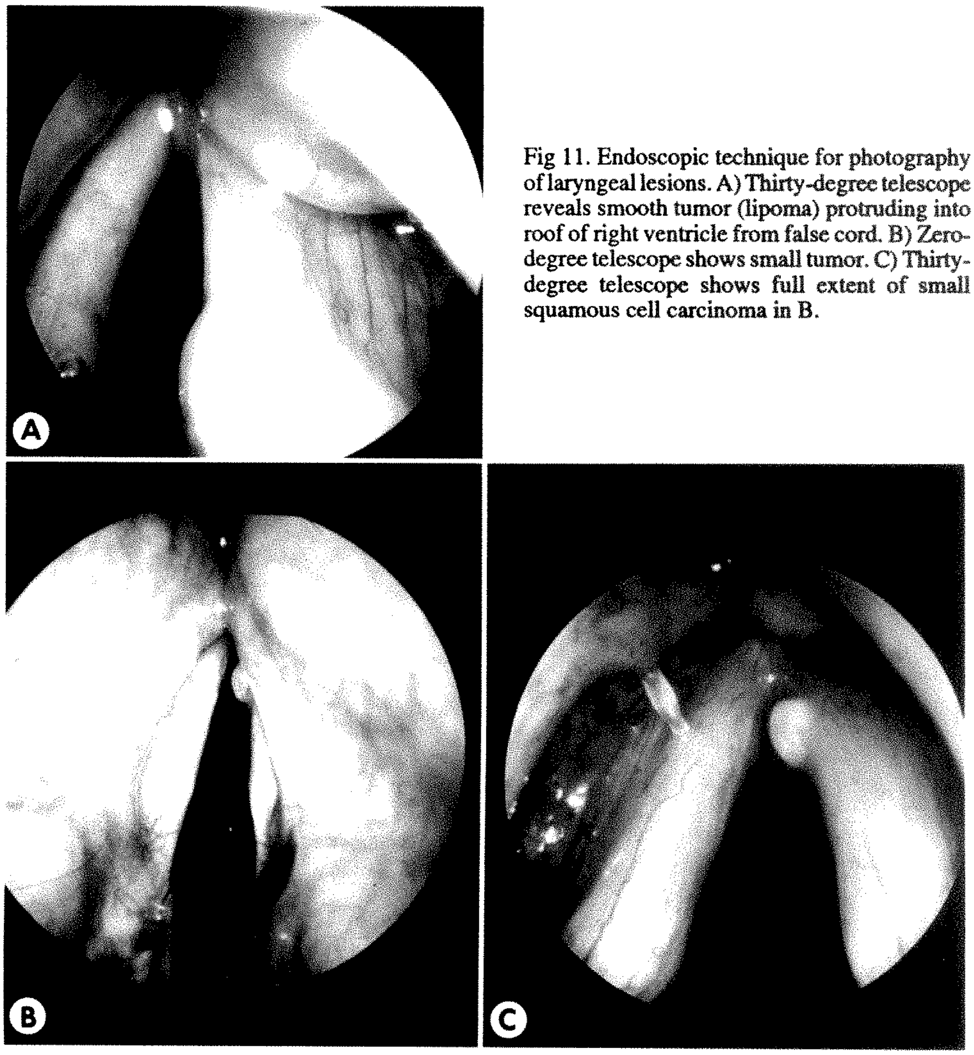

Fig 11. Endoscopic technique for photography of laryngeal lesions. A) Thirty-degree telescope reveals smooth tumor (lipoma) protruding into roof of right ventricle from false cord. B) Zero-degree telescope shows small tumor. C) Thirty-degree telescope shows full extent of small squamous cell carcinoma in B.

an assistant to hold the head and neck.

Photography should, where possible, be performed with no anesthetic tube or with a very small, narrow-diameter tube. A cuffed endotracheal tube, even the smallest microlaryngoscopy tube, is a partial obstruction and obscures the posterior glottic and subglottic spaces.

In adults good conditions for photography are provided by a relaxant anesthetic technique with jet ventilation, either through the 2.8-mm outside diameter Benjet intratracheal tube or through a proximal jetting cannula firmly attached within the proximal lumen of the laryngoscope (Fig 7). When a proximal jet cannula is being used, intermittent jetting can be stopped temporarily for photography so that there is no movement that might blur the photograph.

In children excellent photographic conditions are provided by an inhalational technique using insufflation of halothane, nitrous oxide, and oxygen that requires no endotracheal tube (Fig 6A). With all techniques topical local anesthesia is applied to the mucous membranes of the larynx and upper trachea.

Photography must *never* put the patient at risk. Anesthesia and photography in inexperienced hands could jeopardize the patient's safety, but this situation must not be allowed to occur.

PHOTOGRAPHIC TECHNIQUE

A laryngoscope, selected for maximum exposure of the larynx to clearly display the anatomic lesion, is positioned at naked eye laryngoscopy and suspended by a laryngoscope holder so that the endoscopist is free to use both hands for photography (Fig 2). As an alternative, photography can be achieved with a laryngoscope held in the left hand while the camera and the telescope are controlled by the right hand, but manipulation of the zoom lens and the focusing mechanism is awkward. The control can be preset or adjusted by a second person. It is usually more convenient to have a suspension laryngoscope in place so that two hands can be used. To avoid fogging of the cold telescope when it is first introduced, a

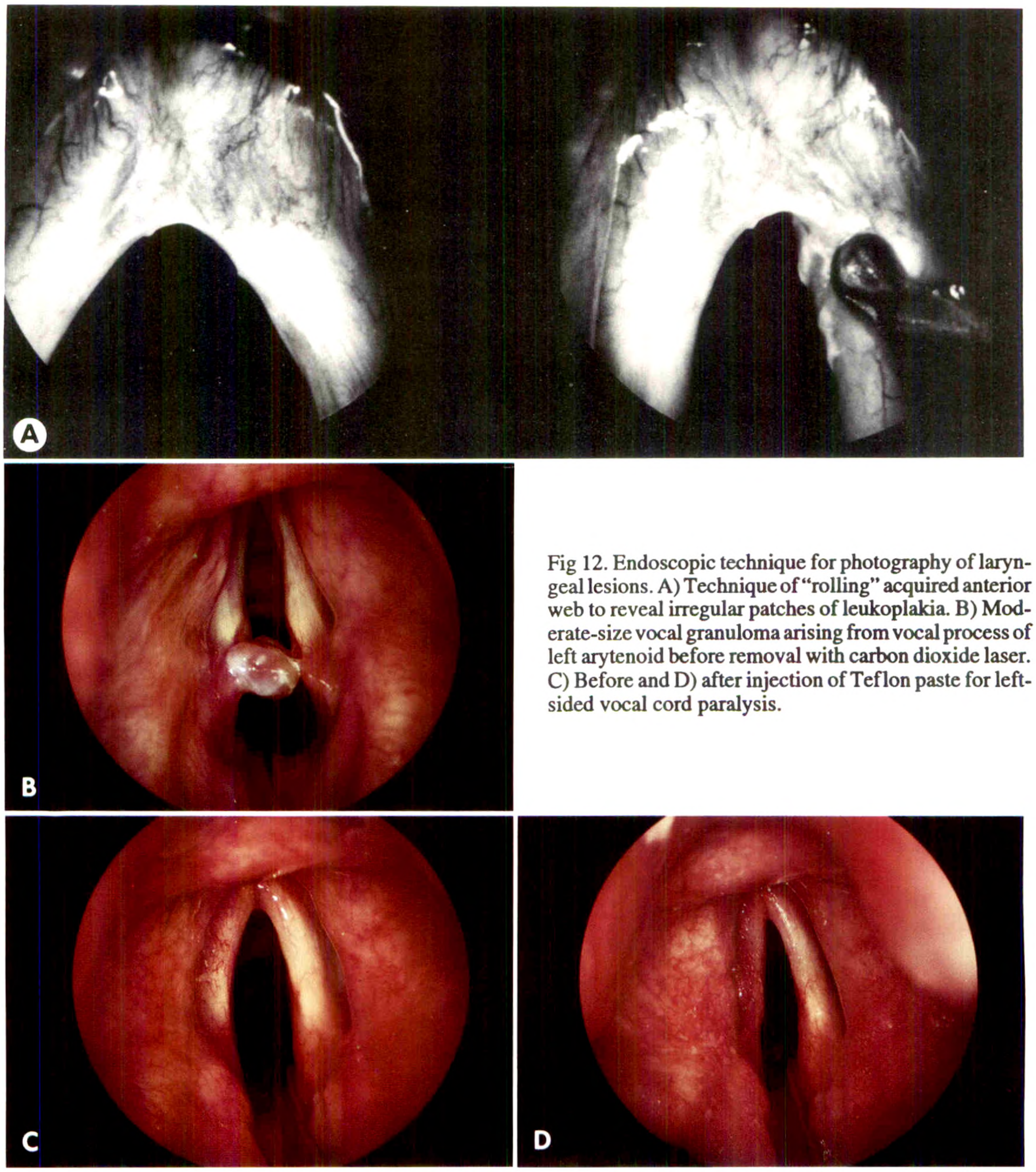

Fig 12. Endoscopic technique for photography of laryngeal lesions. A) Technique of "rolling" acquired anterior web to reveal irregular patches of leukoplakia. B) Moderate-size vocal granuloma arising from vocal process of left arytenoid before removal with carbon dioxide laser. C) Before and D) after injection of Teflon paste for left-sided vocal cord paralysis.

demisting solution can be used, or the tip can be dipped in warm water before use.

A telescope appropriately selected for its length, diameter, and angular view is fitted to the front of the zoom lens, and a light cable is connected to the telescope from the TTL flash unit. With a finger or fingers placed on the anterior neck to apply external pressure and with gentle internal counterpressure from the beak of the laryngoscope, the laryngeal structures are manipulated or rotated to better display the false vocal cords, ventricles, or subglottic larynx and the lesion. All photographs are taken with the shutter speed set on $^1/_{15}$ of a second. The focal length is chosen between 70 and 140 mm, and during uninterrupted visualization of the larynx through the viewfinder of the SLR camera, the focus is finely adjusted, the composition is optimized, and, finally, the shutter is activated — a process usually taking less than 30 seconds.

Photographs can be taken by using an optical device to split the observed image — a "beam splitter." The Wittmoser multiarticulated optical arm has four joints and five segments. Its dual beam splitter can be changed from 50%/50% for examiner and observer to 10%/90% for documentation using a 35-mm still camera, a movie camera, or a television camera. The superb image quality ensures that little detail is lost by transmission through the additional

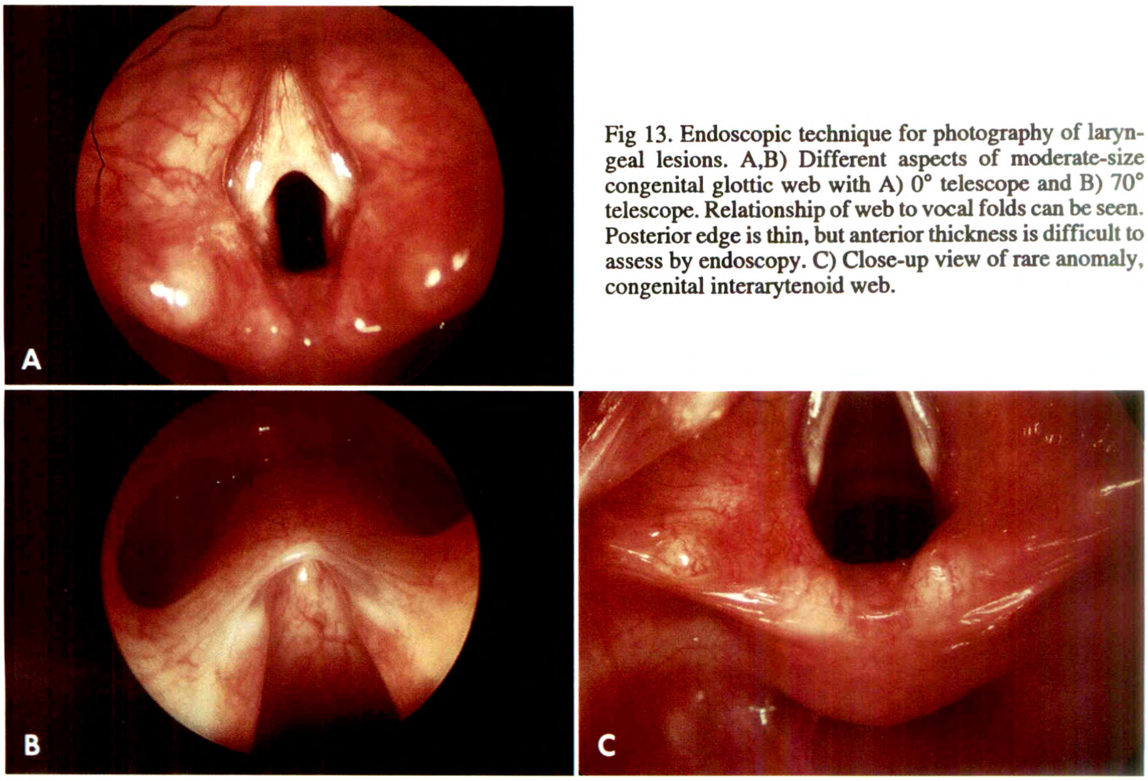

Fig 13. Endoscopic technique for photography of laryngeal lesions. A,B) Different aspects of moderate-size congenital glottic web with A) 0° telescope and B) 70° telescope. Relationship of web to vocal folds can be seen. Posterior edge is thin, but anterior thickness is difficult to assess by endoscopy. C) Close-up view of rare anomaly, congenital interarytenoid web.

five Hopkins rods to the camera. The advantage of this system is that there is no interference at any time to the view of the endoscopist.

Photography of the subglottic region, trachea (Fig 8), carina, and main bronchi is an extension of laryngeal photography and can be accomplished most easily while the suspension laryngoscope is in place by using a longer, 30-cm telescope, either 4.0 or 5.0 mm in diameter. Use of a bronchoscope is seldom necessary except, for example, with an inhaled foreign body or where there is tracheal compression or collapse.

With the same equipment, the cooperation of the patient, and use of topical anesthesia, telescopic still photography can be accomplished in the office by means of the TTL computer flash unit. The best results are with a wide-diameter indirect rigid laryngopharyngoscope such as the Berci-Ward laryngopharyngoscope (Karl Storz 8702K), the telelaryngopharyngoscope (Karl Storz 8704K) with 4x magnification and a focusing device, the Stuckrad magnifying laryngopharyngoscope (Wolf), or the Nagashima SFT-1 right-angled telescope with an integral light transmission cable. These rod telescopes are about 10 mm in diameter. The strobolaryngoscope telescope (Karl Storz 8706CJ; outside diameter 8.5 mm) has a 70° angle to provide a better view of the anterior commissure and is recommended for diagnostic and photographic laryngoscopy in the office.

Many variables affect the overall appearance and impact of the photograph. Are the colors pleasing? Is the image in sharp focus? Is the exposure correct? Even though exposure is "automatic," the presence of a dark central glottic triangle can sometimes result in overexposure of the surrounding tissues. Can the viewer readily orient the picture and identify the features? Is the pathologic change easy to see, preferably allowing comparison of a normal side to an abnormal side? If there is distortion of the larynx, are there recognizable reference points? Symmetry and centering of the image are important. From one photograph to another, the laryngologist should strive for consistency. When the Kantor-Berci laryngoscope provides adequate visualization, the fixed telescope for documentation always gives the same field — very useful in showing the sequence of an operative procedure.

The usual format of endoscopic photographs has been circular. Now, with high-definition close-ups (Fig 9), some become rectangular, but the classic circular shape is used by most photographers.

The normal laryngeal anatomy, viewed with various telescopes, is familiar to the endoscopist (Fig 10).

Photography can be used to illustrate points in endoscopic technique. Unsuspected disorders in otherwise "hidden" parts of the ventricle (Fig 11A) can be discovered and small lesions seen more clearly (Fig 11B,C) when the angled telescopes are used. Figure 12A shows small but important changes hid-

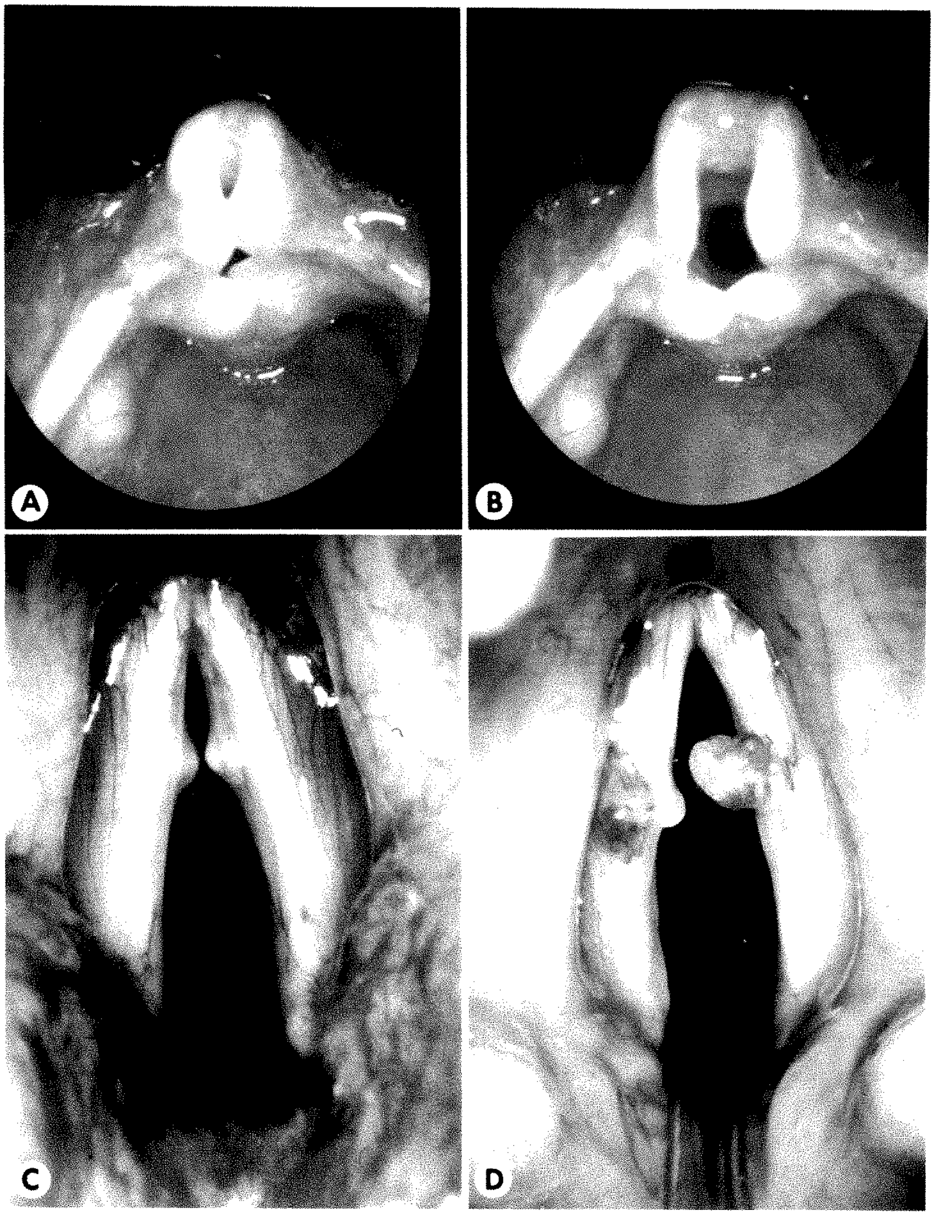

Fig 14. Endoscopic technique for photography of laryngeal lesions. A) Inspiratory and B) expiratory phases of laryngomalacia show cause of inspiratory stridor. Video recording shows dynamic laryngeal changes more vividly. C) Usual appearance of vocal nodules contrasts with D) atypical appearance in woman in her thirties who had refused to have treatment for many years.

ing under the edge of an acquired web. Figure 12B shows the typical site of a vocal granuloma before laser removal. The hemilarynx can be photographed before and after Teflon injection for augmentation and medialization (Fig 12C,D). A congenital glottic web takes on a different perspective when seen with a 0° (Fig 13A) or a 70° (Fig 13B) telescope, and the abnormality in a congenital interarytenoid web can be seen in detail (Fig 13C). The inspiratory (Fig 14A) and expiratory phases of laryngomalacia (Fig 14B) clearly explain the cause of stridor. The contrast between typical vocal nodules (Fig 14C) and atypical changes (Fig 14D) is graphic. Representation of the subglottic edema of croup (Fig 15A) and the frightening supraglottic obstruction of acute epiglottitis (Fig 15B,C) in photographic form is unequaled for teaching.

SUMMARY

Many methods have been used successfully for both black-and-white and color 35-mm single frame laryngeal photography. The most reliable and versatile system for good-quality documentation uses a 35-mm single frame SLR camera with Hopkins telescopes and a synchronized automatic exposure electronic flash generator. Consistently reproducible photographs taken under both good and bad conditions by both the expert and the novice are a practical reality, and in experienced hands the system is relatively safe for the patient, even in small infants or where there is partial airway obstruction.

For best results the endoscopic photographer should have a good knowledge of the normal and pathologic anatomy, of the optical principles of the system, and

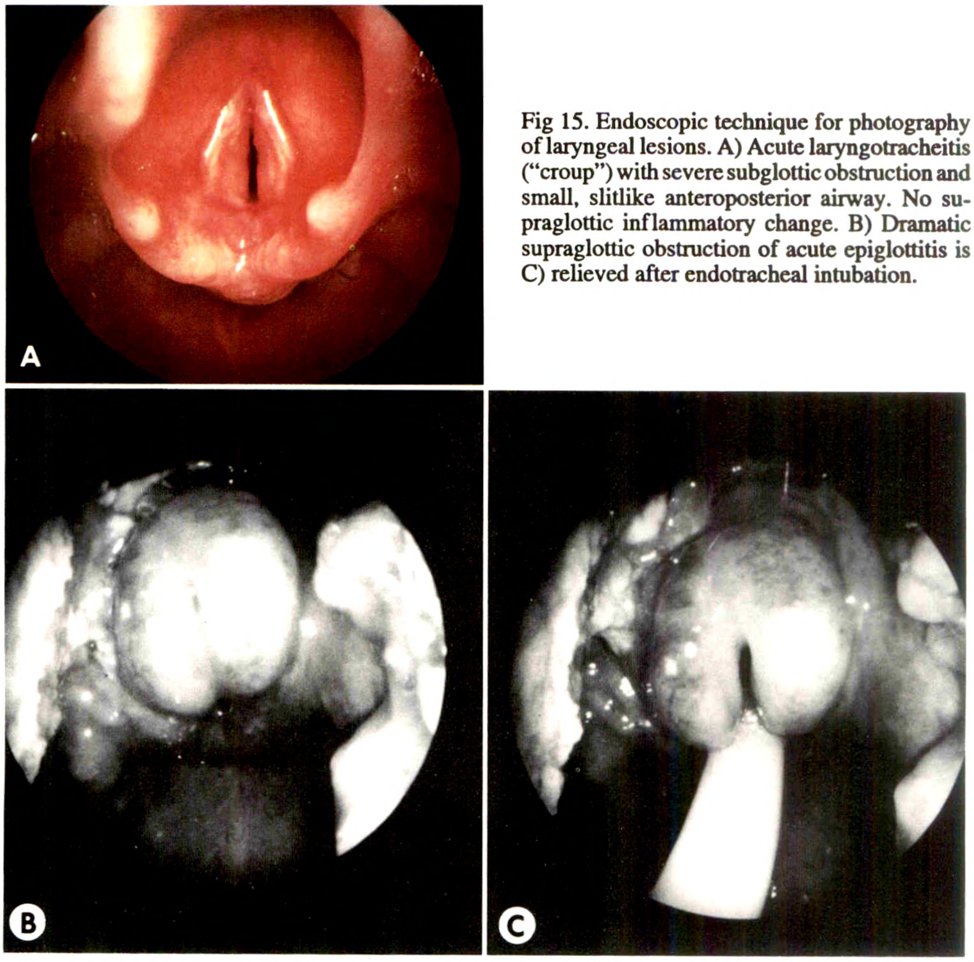

Fig 15. Endoscopic technique for photography of laryngeal lesions. A) Acute laryngotracheitis ("croup") with severe subglottic obstruction and small, slitlike anteroposterior airway. No supraglottic inflammatory change. B) Dramatic supraglottic obstruction of acute epiglottitis is C) relieved after endotracheal intubation.

of the photographic equipment.

The choice of equipment for the individual laryngeal surgeon depends on his or her needs, his or her ability to use the equipment successfully, and the cost. With the latest equipment, routine photographic documentation of any area accessible to a telescope is a practical reality. Exposure is automatic, close-up photography is possible, and the Hopkins telescopes allow a wide latitude in the depth of focus. Documentation offers positive proof, for example, to the oncologist consulted for treatment of malignancy. For teaching purposes the image quality with natural color reproduction of 35-mm photography cannot be equaled. Laryngeal photography is an interesting, exciting, and beautiful representation of both normal and diseased airways.

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REQUEST FOR PROPOSALS AMERICAN LARYNGOLOGICAL ASSOCIATION

The American Laryngological Association has established a grant for research on laryngology, rhinology, and related subjects. The maximum grant for one year is $15,000. Deadline for submission is June 1, 1993. For the specifics of eligibility and application materials, write to the American Laryngological Association, H. Bryan Neel III, MD, Secretary, 200 First Street SW, Rochester, MN 55905.

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NEW PERSPECTIVES IN OTOLARYNGOLOGY–HEAD AND NECK SURGERY

This international symposium, to be held July 5-8, 1993, at St Thomas's Hospital, London, England, will be sponsored by Harvard Medical School, Beth Israel Hospital–Brigham & Women's Hospital, Guy's and St Thomas's Medical and Dental School, and the Université René Descartes Faculté de Medicine, Necker Enfants Malades, Hopital Laennec. For further information, contact Harvard Medical School, Department of Continuing Medical Education, PO Box 825, Boston, MA 02117; phone (617) 432-1525.

Ann Otol Rhinol Laryngol 102:1993

TEFLON INJECTION: POINTERS AND PITFALLS

ROBERT B. LEWY, MD
CHICAGO, ILLINOIS

Our objective is to clarify the procedure used in a series of 335 cases of injection of paralyzed vocal cords. Over 29 years, questions have arisen about the procedure, mostly from trainees. They relate to timing, indications, method, and follow-up. Results of the procedure, when properly performed, have been highly successful. Where indications are appropriate, injection is usually uncomplicated, relatively safe, and done with minimum instrumentation. This is our response, in a question-and-answer format, to the most frequent queries.

KEY WORDS — injection, paralysis, Teflon, vocal cord.

Most residency training programs provide limited opportunities for trainees to observe or perform corrective injection of a Teflon-glycerin mixture to the paralyzed vocal cord. The seeming simplicity of the procedure may lead to a false sense of ease and security, and thus to occasional inaccuracy.

Questions and answers have arisen over time that emphasize problems relevant to indications, techniques, timing, and the close postoperative observation needed to maximize favorable results. Examples of these recurring problems, in a question-and-answer format, are dealt with here.

Q. *When is injection of the vocal cord indicated?* A. In simple idiopathic cases (17%), wait 6 months. Without treatment, the vocal cord may drift back to the midline and function adequately. If the gap is wide, and the patient is aspirating, perform the procedure soon, to protect pulmonary function and to prevent pneumonia.

Q. *When should one proceed with minimal delay?* A. If the patient has progressive disease, such as pulmonary malignancy or an enlarged heart (Ortener's syndrome), and has no expectation of spontaneous cure, the procedure should not be postponed.

Q. *Should the anterior third of the vocal cord be injected?* A. Rarely (done only twice in this series).

Q. *Is there a risk of overinjection?* A. Yes. Tailor the pants to fit the customer. Always inject less rather than risk using too much. If you do overinject, however, the 50% glycerin in the mixture absorbs within 4 days and thus may save the day and aid in producing favorable results.

Q. *How important is the position of the tip of the laryngoscope?* A. This is of the utmost importance. The positioning depends in part on the size and shape of the paralyzed cord, and the size and degree of obstruction caused by the false vocal cords. One should usually go in at a slight angle to the cord. Position the tip about 2 mm from the cords, proximally, but never between or beyond the cords. Do not use gear or lifting power to put the nonparalyzed cord on stretch. Leave it freely moveable.

Q. *Where should the first injection go?* A. It should be about 3 mm deep at an outward angle, and about 2 mm lateral to the place of greatest curvature or gap.

Q. *Where does the second injection go?* A. About 4 to 6 mm posterior to the first.

Q. *What is the next step?* A. Have the patient phonate. Listen for an improved clarity of sound. This is as important as observing the closure of the gap. If there is difficulty in closing the posterior third of the cord, don't overload. (For some reason this is a frequent error.) We have seen many excellent phonatory and aspiration prevention results despite incomplete closure of the posterior third.

Q. *What are the results when an arytenoid has fallen forward on the paralyzed side and consequently the cords are at different levels?* A. Occasionally, there are excellent results even when this occurs. On average, however, poorer results may be experienced and this could be an indication for the older Meurman operation or the Isshiki modification.

Q. *Is the injection procedure reversible?* A. Yes, although to my knowledge only one in this series has been reversed.

Q. *Is the microscope useful?* A. No. It obstructs the instrumentation.

Q. *How many patients had respiratory obstruction*

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Presented at the meeting of the American Laryngological Association, Palm Desert, California, April 11-12, 1992.

REPRINTS — Robert B. Lewy, MD, 5532 South Shore Dr, Chicago, IL 60637.

requiring tracheotomies? A. Three, or less than 1%.

Q. *What measures are used to minimize postoperative reactions?* A. Steroids are routinely administered: prednisone 2.5 mg (tapered over 4 days from four times per day to three, two, and one).

Q. *How long are patients hospitalized?* A. Three days postoperatively.

Q. *Do you make tape recordings of the voices before and after surgery?* A. Yes, and occasionally other special studies, such as spectroscopic pictures of the tapes.

Q. *Is voice improvement the only criterion of success?* A. No. The larynx is a valve of many functions, and improving its overall competence is essential. We try to improve breath control; speech quality and control; and ability to cough, to strain, and to laugh — not just smile.

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FUNCTIONAL SINUS TECHNIQUES

An international course on functional sinus techniques will be held in Graz, Austria, September 2-4, 1993. It will be conducted in English. For further information, contact Prof Dr Heinz Stammberger, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; telephone 43-316-385-3448; fax 43-316-385-3425.

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4TH INTERNATIONAL ACADEMIC CONFERENCE
IMMUNOBIOLOGY IN OTOLOGY, RHINOLOGY AND LARYNGOLOGY

The 4th international academic conference Immunobiology in Otology, Rhinology and Laryngology will be held in Oita, Japan, April 4-7, 1994. For further information contact Goro Mogi, MD, Dept of Otolaryngology, Oita Medical University, Hasama-machi, Oita 879-55, Japan; telephone 81-975-49-4411 ext 2912 or 2913; fax 81-975-49-0762.

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PENDRED'S SYNDROME

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Although 5% of all cases of congenital deafness are caused by Pendred's syndrome, there are few reports in the literature. Seven patients with Pendred's syndrome in three families living in the same village were detected. For that reason, the syndrome is reviewed in light of the literature. The sex distribution of the patients with Pendred's syndrome and their families was recorded. We tested for thyroxine, triiodothyronine, thyroid-stimulating hormone, triiodothyronine resin uptake, and perchlorate, and performed caloric testing. In one patient, subtotal thyroidectomy was performed. In the histopathologic study, a thyroid nodule filled with colloid was found. Chromosome studies showed no anomalies in any patient. Five of the patients were deaf-mutes. We observed that the parents were cousins in all three families. These families also had healthy children, and the existence of the syndrome in both sexes points to an autosomal recessive trait.

KEY WORDS — Pendred's syndrome.

INTRODUCTION

Pendred's syndrome of congenital deafness is not to be confused with the deaf-mutism seen in endemic cretinism or with the minor impairment of hearing that may be found in severely hypothyroid persons. Pendred's syndrome is one of the most frequent entities among 124 syndromes involving genetically transmitted deafness.[1-5] Tests for perchlorate and thiocyanate may be diagnostic.

Goiter generally appears in these patients at puberty or later, but may be present in early childhood.[1] It may not be seen in all male patients and tends to relapse after surgery.[4] The cause of the goiter is a deficiency of iodide peroxidase. The enzyme deficiency does not cause deafness. In other words, the goiter and the deafness are different clinical findings due to involvement of the same gene.[5]

Van Wouwe et al[6] published a report on a severely retarded girl with multiple congenital anomalies. Chromosome studies showed a der (8) chromosome with dup(10p) and deficiency for a small distal segment of 8q. At 1 year the patient was also found to have Pendred's syndrome, an autosomal recessive defect in organification.[6] Pendred's syndrome is proven by perchlorate and thiocyanate flush tests.[5,7] A deficiency of thyroxine synthesis occurs, thyroid-stimulating hormone increases, and goitrous enlargement is seen in the thyroid tissue. Most affected persons are clinically euthyroid, but hypothyroidism may ensue even during childhood.[1,2]

Biesalski et al[8] estimated retinol binding protein in the plasma of 91 children with hearing impairment of different causes and 35 normal children of similar age groups; those with Pendred's syndrome had values in the lower range of the total distribution curve.

Mondini dysplasia of the inner ear has been determined in 50% of patients with Pendred's syndrome: namely, defects in the bony and membranous labyrinths, organ of Corti, and stria vascularis. Temporal bone studies have shown hyperostosis of the promontory and round window.[9-11] Johnsen et al[12] investigated the inner ears of five adult patients with Pendred's syndrome by using computed tomography. They found typical Mondini malformations of the cochlea in all patients. The acoustic nerve was intact. However, each element of the inner ear had an abnormality.[9] An atypical and hyperplastic appearance has been determined in the thyroid gland.[1] Thyroid carcinoma has been reported in a patient with Pendred's syndrome.[10]

CASE REPORTS

Patients 1, 2, and 3. This family (G family) is living in Tasobasi village, Tarsus, Turkey. The father and mother are cousins. The family has nine children (three male and six female). The oldest child (patient 1) was a 21-year-old woman (see Figure). The third child (patient 2) was a 19-year-old woman. The sixth

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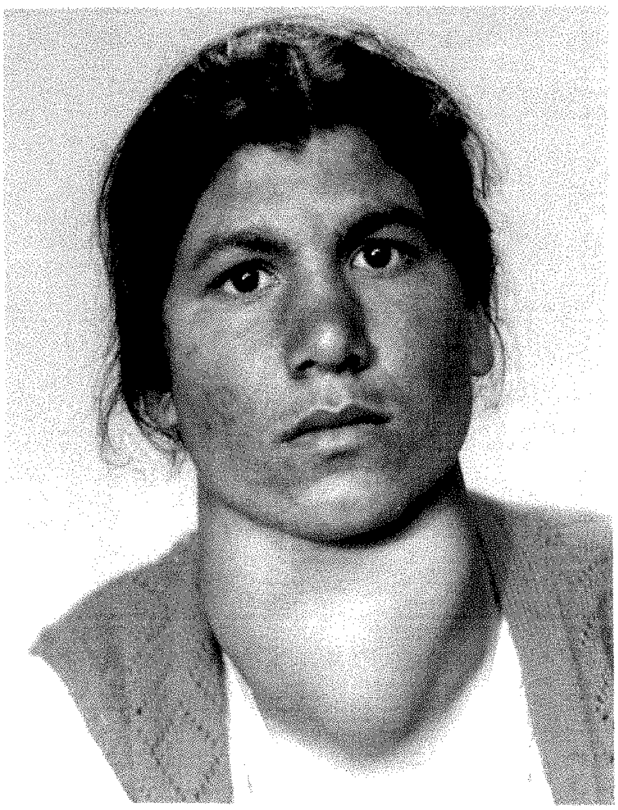

(Patient 1) Woman with Pendred's syndrome.

child (patient 3) was a 10-year-old boy. These children had goiter and deaf-mutism. The other six children were normal.

Tasobasi village is in an endemic goiter region. Because endemic goiter and deafness may occur separately, the other siblings were examined. The second child (male) had a hypertrophic thyroid gland on palpation, with deafness and diffuse thyroid hyperplasia on scintigraphy. Perchlorate testing was applied to these four siblings. All patients with mutism had positive results, but the test of the second child was negative. Caloric testing showed hypoexcitability in these four siblings.

Patients 4 and 5. The K family also lived in Tasobasi village. The father and mother were cousins and had six children (four female). Of these children, two had goiter and deaf-mutism and positive perchlorate testing (patient 4, a 38-year-old woman, and patient 5, a 33-year-old woman). Total hearing loss was found by audiometric testing. The caloric response showed unexcitability.

Patients 6 and 7. Family A also lived in the same village. Patient 6 was an 18-year-old man and patient 7 was a 22-year-old man. Patient 6 had goiter and deaf-mutism. There was a cold nodule (4 x 5 cm) in the right thyroid lobe, and subtotal thyroidectomy was performed. The thyroid nodule was filled with colloid on histopathologic examination. Patient 7 had a moderate sensorineural hearing loss and goiter. The perchlorate test was positive, and the caloric response showed unexcitability. The father and mother of these patients were third-degree cousins. The siblings (four female and three male) were normal.

TABLE 1. MALE TO FEMALE RATIOS OF PATIENTS AND THEIR FAMILIES

Family	*Patients*	*Healthy Siblings*	*Total*
G	1/2	2/4	3/6
K	0/2	2/2	2/4
A	2/0	3/4	5/4
Total	3/4	7/10	10/14

The sex distribution of the patients with Pendred's syndrome and their families is listed in Table 1. Laboratory data are listed in Table 2.

DISCUSSION

Pendred's syndrome has been discussed by other authors since Vaughan Pendred[13] first described this entity in 1896 in two sisters who were deaf-mutes and had severe goiter.[1,2,11] All publications have mentioned that the disease is an autosomal recessive trait.[1,2,4,10] In our series, we observed that the father and mother were cousins in the three families. These three families also have healthy children, and the existence of the syndrome in both sexes points to an autosomal recessive trait.

There are few reports of histopathologic findings of this syndrome.[8,9] Hvidberg-Hansen and Jørgensen[11] reported in 1968 that patients with Pendred's syndrome had an endemic goiter in thyroid specimens, with Mondini dysplasia of the inner ear. One patient had cystic nodular goiter that was found by ultrasound. Six patients had diffuse hyperplasia in our series, but histopathologic examination could not be performed because the patients were not operated upon.

Patients with Pendred's syndrome can be clinically euthyroid or hypothyroid.[2,10,12] We found lower serum levels of triiodothyronine, thyroxine, and triiodothyronine resin uptake and higher serum levels of thyroid-stimulating hormone, except in one patient in family G, who had normal levels (Table 2). However, this patient had serum triiodothyronine and thyroxine levels at the lower limits of normal and serum thyroid-stimulating hormone levels at the higher limits of normal.

Morgans and Trotter[14] reported in 1958 that patients with Pendred's syndrome were normal in terms of psychologic and mental conditions. Our patients

TABLE 2. LABORATORY FUNCTION TESTS IN PATIENTS

Family	*Patient*	*T4 (g/dL)*	*T3 (mg/mL)*	*TSH (μ/mL)*	*T3 RU (%)*	*Perchlorate Testing*	*Caloric Response*
G	1	0.6	42	72	21.8	Positive	Hypoexcitable
	2	5.8	73	8	23.2	Positive	Hypoexcitable
	3	0.4	38	160	20.1	Positive	Hypoexcitable
K	4	2.1	45	60	22.9	Positive	Unexcitable
	5	1.0	32	48	24.0	Positive	Unexcitable
A	6	2.4	39	852	5.6	Positive	Unexcitable
	7	2.8	61	732	5.3	Positive	Excitable
Normal values		5.0-13.7	75-175	10	22-37	Negative	Excitable

T4 — thyroxine, T3 — triiodothyronine, TSH — thyroid-stimulating hormone, T3 RU — T3 resin uptake. All these analyses were by radioimmunoassay (Diagnostic Products Corp, USA).

were similarly normal, except patient 5, who is aggressive and discordant with her surroundings. Morgans and Trotter have recorded that the ratio of female to male patients was 8 to 12 in 20 patients with Pendred's syndrome, who had 11 male and 12 female healthy siblings among them. Our 7 patients with Pendred's syndrome (4 female and 3 male) have 17 healthy siblings (10 female and 7 male; Table 1).

Hvidberg-Hansen and Jørgensen[11] reported that the incidence of the syndrome in the British population is 1 in 13,000. Bergstrom[2] and Meyerhoff and Liston[15] have reported that the autosomal recessive gene is found in 1 of every 150 to 500 persons and may be the cause of up to 10% of all cases of congenital deafness. The bilateral hearing loss in Pendred's syndrome is present at birth, as a moderate loss in the high frequencies.[2] Six of our patients had mutism secondary to total hearing loss. Although Bergstrom[2] has reported that male patients may lack a goiter, 1 of our series had diffuse goiter and another had a nodular goiter. Caloric testing has revealed a hypoactive vestibular labyrinth in most patients with Pendred's syndrome.[11] In our series, 3 patients had hypoexcitable caloric responses and 3 patients had no responses (Table 2).

Van Wouwe et al[6] reported that the chromosomal gene location is not yet known, and deletions have occasionally proved to be of help in gene mapping. The combination of a chromosome defect and a major gene defect by pure chance alone may not be rare, but can be easily overlooked because of the overwhelming somatic manifestations of a chromosome imbalance. Van Wouwe et al recommend evaluation of hearing and thyroid function in other patients with 8q24 deletions. We have found a major chromosome defect in another form of Pendred's syndrome that has different symptoms and signs, and we are going to publish this finding as soon as possible.

Since Pendred's syndrome is of autosomal recessive origin, we recommend that marriages between relatives be discouraged. The ratio of female to male patients is low in the literature; our ratio is 4 to 3. However, since our series does not include many patients, we are not able to test the statistical significance. In addition, although it has been reported in the literature that the ratio of healthy siblings to patients is low, this ratio was 17 to 7 in our series. This finding indicates that there might be many more healthy persons with the chromosome abnormality than patients with Pendred's syndrome.

ACKNOWLEDGMENT — Osman Demirhan, FD, Department of Medical Biology, Çukurova University, performed the chromosome studies.

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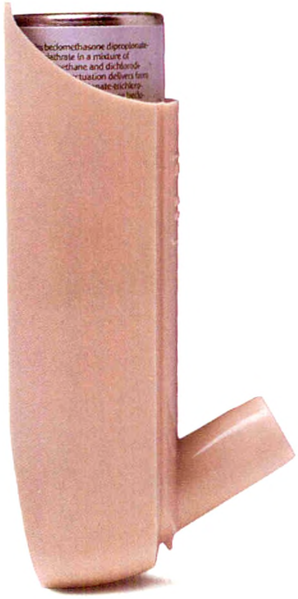

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Please see next page for brief summary of full Prescribing Information.

VP-363/17551809 3/93

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BRIEF SUMMARY
(For full Prescribing Information see package insert)

INDICATIONS AND USAGE VANCENASE POCKETHALER Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

VANCENASE POCKETHALER Nasal Inhaler is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies in seasonal and perennial rhinitis have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Although systemic effects are minimal at recommended doses, VANCENASE treatment should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. VANCENASE treatment should not be used in the presence of untreated, localized infection involving the nasal mucosa.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE POCKETHALER Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients, previously treated for prolonged periods with systemic corticosteroids, are transferred to VANCENASE POCKETHALER Nasal Inhaler. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Extremely rare instances of nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE POCKETHALER Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE POCKETHALER Nasal Inhaler may suppress HPA function.

VANCENASE treatment should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE POCKETHALER Nasal Inhaler to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE Nasal Inhaler should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of the VANCENASE product into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE treatment over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrus cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrus cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE POCKETHALER Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes. Adverse reactions reported in controlled clinical trials and in long-term open studies in patients treated with VANCENASE Nasal Inhaler are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of VANCENASE Nasal Inhaler have been reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children.

Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely. (See **PRECAUTIONS**.)

Transient episodes of epistaxis or bloody discharge from the nose have been reported in 2 per 100 patients.

Ulceration of the nasal mucosa has been reported rarely.

Extremely rare instances of nasal septum perforation have been reported following the intranasal application of aerosolized corticosteroids. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm have been reported following the oral and intranasal inhalation of beclomethasone.

Increased intraocular pressure has been reported rarely. (See **PRECAUTIONS**.)

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome could occur.

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One canister of VANCENASE POCKETHALER Nasal Inhaler contains 8.4 mg of beclomethasone dipropionate; therefore acute overdosage is unlikely.

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INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients being treated with VANCENASE AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use VANCENASE AQ Nasal Spray at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of VANCENASE AQ Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions carefully.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild, transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

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Ann Otol Rhinol Laryngol 102:1993

COMPARISON OF FUNCTIONAL ENDOSCOPIC SINUS SURGERY UNDER LOCAL AND GENERAL ANESTHESIA

PAUL D. GITTELMAN, MD
JOSEPH B. JACOBS, MD
JANE SKORINA, MD
NEW YORK, NEW YORK

We present a retrospective comparison of intravenous sedation and general anesthesia techniques employed at New York University–Bellevue Medical Center for functional endoscopic sinus surgery. Some authors have stressed the use of local anesthesia with intravenous sedation in order to avoid complications and reduce blood loss. We have reviewed 232 patients who underwent 401 consecutive ethmoidectomies and maxillary antrostomies. Local anesthesia, employed in 64% of patients, carried an estimated blood loss of 23 mL per side. General anesthesia was associated with an average blood loss of 58 mL per side. The rate of operative complications for local anesthesia was 8.7% per patient, with a 1.6% rate of major complications per side. General anesthesia carried an overall complication rate of 2.4% per patient, with no major complications. General anesthesia is a relatively safe and viable option for endoscopic sinus surgery that in selected cases may be preferable to local anesthesia.

KEY WORDS — anesthesia, functional endoscopic sinus surgery.

INTRODUCTION

The functional approach to sinus disease and endoscopic surgical procedures have gained widespread acceptance among otolaryngologists. These techniques enhance our ability to treat both limited and widespread sinus disease by providing excellent illumination and visualization. Recent publications concerning endoscopic sinus surgery detail patient evaluation, surgical technique, and perioperative management, as well as results and complications.[1-9] An advantage of endoscopic techniques is the ability to utilize local anesthesia in an outpatient setting.

In some patients suffering from chronic sinusitis, general endotracheal anesthesia may be required. This paper is a retrospective review of 401 consecutive ethmoidectomies on 232 patients performed by the senior author (J.B.J.) at New York University Medical Center from January 1989 through March 1991. Specific attention has been directed toward establishing the safety and reliability of performing the surgical procedure under general anesthesia. Operative time, estimated blood loss (EBL), and the incidence of major and minor complications will be discussed.

METHODS AND MATERIALS

During the 27-month period from January 1989 through March 1991, the senior author performed 401 endoscopic ethmoidectomies on 232 patients at New York University Medical Center. Hospital and office charts as well as the anesthetic records were reviewed and information was extracted as to the extent of surgery, type of anesthesia, EBL, time of surgery, complications, and prior surgical and medical history. The EBL was obtained from the surgeon's dictation or operative note. The operative time came from either the anesthesia record or the operating room nurse's flow sheet and included the surgical time as well as all anesthetic manipulation, including patient preparation, induction, intubation, and emergence from anesthesia through extubation.

Patients were categorized according to the use of local or general anesthesia, unilateral or bilateral procedures, and an inpatient or outpatient setting for the surgery. Three types of anesthetic techniques were used: 1) local-standby (LSB), with an anesthetist providing monitoring and sedation, 2) general endotracheal anesthesia (GET), and 3) "switch," involving converting from LSB to GET during the procedure. This was necessary in a small percentage of patients who could not tolerate the procedure under local anesthesia. These patients were uncooperative because of discomfort, anxiety, or inadequate sedation or had labile blood pressure with wide fluctuations. Anesthetic choice was based primarily on the medical condition of the patient, the extent of disease, the perceived ability of the patient to cooperate, the revision nature of the surgery, and patient preference. The presence of reactive airway disease, labile hypertension, or gross polypoid disease, especially with a history of multiple previous nasal or sinus procedures, often led to the selection of general anesthesia as the modality of choice.

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The largest subset of patients underwent same-day admission into the hospital, overnight observation, and discharge the following day. Patients with ongoing medical problems, reactive airway or cardiac disease, or postoperative medical problems occasionally stayed 1 or more additional days. The ambulatory surgery scenario necessitated the careful selection of patients who were unlikely to require overnight in-hospital observation.

All patients underwent preoperative evaluation with computed tomography in the coronal plane and diagnostic endoscopy. Initial operative plans were modified on the basis of the intraoperative findings and the condition and response of the patient. The Messerklinger[1] technique was employed with an anterior to posterior dissection. Suprainferior turbinate antrostomies were routinely performed. Additional procedures were performed when necessary, especially in those patients with more pronounced disease or with coexisting anatomic abnormalities. These may have included submucous resection, Caldwell Luc, sphenoidotomy, partial middle turbinectomy, frontal sinusotomy, lysis synechiae, reduction of fracture, frontal trephination, or potassium-titanyl phosphate laser treatments. Severity of disease also factored into the selection of anesthetic technique, whereby patients who might require more extensive procedures were more likely to be inpatients and undergo general anesthesia.

RESULTS

The age range of our 232 patients was 9 to 83 years, with an average of 50 years. There were 123 males with an average age of 49 (9 to 83) years and 109 females averaging 43 (11 to 80) years.

Four hundred one ethmoidectomies (sides) were performed. Overall, EBL was 36 mL and operative time was 52 minutes per side. Two hundred fifty-six sides (149 patients) were done under LSB with an EBL of 23 mL and time of 49 minutes per side. The remaining 145 sides (83 patients) underwent GET (including those switched intraoperatively) with EBL and time of 58 mL and 79 minutes, respectively.

Sixty-three patients underwent unilateral procedures with an overall average EBL of 41 mL and an average operative time of 90 minutes. Of this group, 21 patients underwent general anesthesia; the average EBL was 61 mL and the average time was 121 minutes. The remainder underwent local anesthesia with an average EBL of 32 mL and time of 74 minutes.

When bilateral procedures were performed (169 patients), the average EBL was 68 mL and the operative time averaged 112 minutes. Forty-seven patients in this group underwent GET; EBL and time were 113 mL and 135 minutes, respectively. One hundred seven patients underwent LSB, with an average EBL of 41 mL and average time of 96 minutes. Fifteen patients required an intraoperative switch from LSB to GET; EBL and time were 125 mL and 165 minutes, respectively.

TABLE 1. AVERAGE BLOOD LOSS, AVERAGE OPERATIVE TIME, AND NUMBER OF PATIENTS BY NUMBER OF SIDES DONE, ANESTHETIC TECHNIQUE, AND INPATIENT OR OUTPATIENT STATUS

Sides	*Anest*	*I/O*	*EBL (mL)*	*Time (min)*	*No. of Pts*
1	G	I	59	129	18
		O	72	78	3
	L	I	35	90	25
		O	27	51	17
2	G	I	116	139	44
		O	77	88	3
	L	I	42	103	83
		O	36	72	24
	S	I	125	165	15

Anest — anesthesia type, G — general, L — local, S — switch from local to general, I — inpatient, O — outpatient, EBL — estimated blood loss.

Forty-seven patients (74 sides) underwent outpatient procedures. Six patients (9 sides) received general anesthesia and 41 patients (65 sides) received local. Inpatient status was given to 185 patients and 327 sides. General anesthesia in this group accounted for 62 patients and 106 sides, while local anesthesia included 108 patients and 191 sides. Switch anesthesia was limited to inpatients and included 15 patients and 30 sides.

Table 1 compares values for EBL and time on the basis of number of sides done, anesthetic choice, and inpatient or outpatient status. Seventy-two patients gave a history of prior nasal or sinus surgery elsewhere. There were 42 asthmatic patients, among whom 15 had prior surgery. Among the asthmatics, 81 sides were done. Thirty-nine of the asthmatics had both sides done: 15 under general anesthesia, 18 under local anesthesia, and 6 switched to general during the procedure. Labile hypertensives accounted for 15 patients. Additional procedures were performed in 147 patients. Revision endoscopic procedures were performed in 9 patients.

Complications are listed in Table 2. There were 11 minor complications and 4 major complications. The overall complication rate was 6.5% per patient and 3.7% (0.9% major) per side. Under LSB 8.7% of patients and 5.1% (1.6% major) of sides developed complications. The complication rate for GET was

TABLE 2. MAJOR AND MINOR COMPLICATION LIST

Complication	*LSB*	*GET*	*Total*
Minor			
Minor postop bleeding	2		2
Periorbital ecchymosis or emphysema	3	2	5
Septal abscess	1		1
Toxic shock–like syndrome	1		1
Ruled-out myocardial infarction	1		1
Asthma attack	1		1
Total minor	9	2	11
Major			
Severe bleeding	4		4
Total complications	13	2	15

LSB — local-standby anesthesia, GET — general endotracheal anesthesia.

2.4% per patient and 1.4% per side. There were no major complications associated with GET. The 4 major complications were all serious epistaxis occurring within the first postoperative month. These four patients had their procedures performed under local anesthesia and were readmitted for treatment and observation. Two were controlled with anterior packs, one required a posterior pack, and the fourth patient was taken back to the operating room (OR) for cautery under endoscopic control. This patient required a blood transfusion.

There were nine patients who exhibited significant blood pressure swings during their procedure. Four were under local anesthesia, two were under general anesthesia, and three were switched to general anesthesia intraoperatively. Six procedures were listed as partial or attenuated because of poor patient tolerance or excessive intraoperative bleeding. Of this group, two were under general and four were under local anesthesia.

DISCUSSION

In the early 20th century, Mosher stated that the intranasal ethmoidectomy is "the blindest and most dangerous [surgical procedure] in all surgery."[10(p31)] He went on to write that "it has proved to be one of the easiest operations with which to kill a patient." Complications associated with this procedure led many surgeons to avoid performing ethmoid surgery even into the middle and later portions of the 20th century. However, the recent introduction of endoscopes, associated with enhanced illumination and visualization, has dramatically improved surgical dissection of the ethmoid sinus. In addition, the functional theory of sinusitis has directed our attention to the clefts and spaces of the middle meatal lateral nasal wall as the primary focus of obstructive sinusitis. This anatomic region is ideally approached with endoscopes and endoscopic surgical techniques.

Despite the risks associated with the procedure, the intranasal ethmoidectomy is indicated for the treatment of chronic sinusitis. Controversy exists concerning the choice of anesthetic techniques for performing endoscopic sinus surgery.[3,11,12] Local anesthesia with sedation is the preferred method at our institution. However, GET may be recommended for asthmatics, when extensive sinus disease is present, or in patients unwilling to be awake and/or aware.

It should be expected and is apparent in our series that general anesthesia increases operative time. Further, the fixed anesthesia overhead time for a particular anesthetic technique renders the overall operative time for bilateral procedures only slightly greater than for unilateral procedures. The additional operative time for general anesthesia is due to added nursing preparation, induction, intubation, and extubation in a residency teaching program.

Also apparent in the data is the increased operative time associated with inpatient versus outpatient procedures. This reflects factors related to increasing disease, as well as the overall medical condition of the patient that required additional anesthesia monitoring or preparation as explained above. Another factor appears to be the degree of nursing preparation required in the inpatient OR compared with our outpatient OR, which may or may not be unique to our institution. Further, the inpatient OR tends to carry more overhead related to anesthesia resident training than the outpatient OR.

There is evidence that the use of general anesthesia may be associated with excessive blood loss.[5,11,12] In our patient population the average blood loss in bilateral procedures was 113 mL under general anesthesia as compared to 41 mL with LSB. The EBL in unilateral surgical cases was 61 mL under general anesthesia and 32 mL with local anesthesia. Additional data reveal consistently higher blood loss for inpatient procedures, reflecting the advanced disease often present in this surgical group. These findings are in general agreement with results from other institutions. Levine[8] demonstrated EBL in his series to be 65 mL or 120 mL when a septoplasty was performed. Schaefer et al[6] reported 77 mL and Hoffman et al[9] reported 129 mL. Stankiewicz[5,7] described a blood loss of 215 mL under local anesthesia and 293 mL under general. Sixty-six percent of the procedures in his series were done under general anesthesia.

Blood loss under general anesthesia can be minimized by the use of reverse Trendelenberg positioning, topical mucosal decongestion prior to meticulous infiltration of 1:100,000 epinephrine with a sufficient delay to allow maximal vasoconstriction, utilizing suction forceps, and the temporary application of thrombin-soaked neurosurgical cottonoids. Hypotensive techniques keeping blood pressure in the range of 80 to 100/60 mm Hg are also helpful. Naturally, the medical condition of the patient must be considered, and this technique should not be used in conjunction with reverse Trendelenberg positioning when there is the potential to seriously affect cerebral blood flow. While we have not encountered any such problems, the potential must be considered.

There is evidence that the use of general anesthesia may be associated with higher complication rates.[5,11,12] Our overall immediate perioperative complication rate of 6.5% per patient and 3.7% (0.9% major) per side is similar to published series of intranasal ethmoidectomy performed with or without endoscopes. Using conventional techniques, Freedman and Kern[13] and Friedman and Katsantonis[14] reported overall complications of 2.8% and 3.7%, respectively. Lawson[15] performed 1,077 nonendoscopic ethmoidectomies in 600 patients, with an overall complication rate of 1.1% and a major complication rate of 0.6% per ethmoidectomy. Using endoscopic sinus surgery, Stankiewicz[5,7] reported a series of 180 patients and 300 ethmoidectomies, with an overall complication rate of 9.3%. The latter 90 patients only carried a 1.4% rate, with 0.7% major complications demonstrating a learning curve for these techniques. Levine[8] reported 0.7% major complications and 8.3% minor complications in 458 procedures on 250 patients. Schaefer et al[6] performed 472 procedures on 100 patients, with 14% minor complications and no major complications. Hoffman et al[9] reported 8% minor and 1% major complications in 129 procedures on 100 patients.

In our series, the use of general anesthesia was not associated with higher rates of complications. There were no patients who developed permanent visual changes, a cerebrospinal fluid leak, epiphora, meningitis, or brain abscess. Four patients were treated for significant postoperative epistaxis with readmission and packing. One patient required transfusion 1 week postoperatively, when he was fully anticoagulated on coumadin. Periorbital ecchymosis or periorbital emphysema, indicative of fracture of the lamina papyracea, developed in five patients: three under local anesthesia and two with general anesthesia. One of these two patients developed some temporary diplopia, probably from trauma to the medial rectus muscle. One additional patient manifested a brief toxic shock–like illness. All of these complications resolved without further sequelae. Interestingly, all but two of these complications occurred under local anesthesia, and none of the patients who underwent general anesthesia developed major complications.

Specific guidelines are followed to avoid operative complications under general anesthesia. The techniques for reducing blood loss discussed above are of paramount importance. If cautery is used, it should be the bipolar type. Suction forceps provide improved operative visualization if bleeding obscures disease. Constant vigilance and attention to detail is paramount when bleeding is encountered. Delaying the surgery or even canceling the procedure must always be considered as a possibility in every case. Thorough preoperative endoscopic evaluation of the intranasal anatomy as well as recognition of computed tomography–documented anatomic variations is required to avoid potential orbital or intracranial trauma. The scan must be present in the OR, and specific sections should be highlighted where anatomic variability exists.

Intraoperative measurements of the distance from the anterior nasal spine to the ethmoid roof or sphenoid face are taken and compared to the patient's lateral radiographs or known averages to orient and alert the surgeon to the proximity of vital boundaries. Visualization of ocular movement may reveal early orbital soft tissue violation. The prompt recognition of periorbital fat in the ethmoid bed, aided by gentle palpation of the globe, will avoid further manipulation and prevent more serious complications from ensuing. Exposed fat should be left alone. Finally, a charge coupling device camera and a monitor provides enhanced detail of the operative site. The addition of a beam splitter will allow direct visualization through the endoscope for comparison.

The retrospective nature of this study may introduce bias in that general anesthesia was preferentially used in those who were sicker or had more extensive or recurrent disease. However, only one third of our patients underwent general anesthesia. Under these conditions, one might expect general anesthesia to manifest increased blood loss, operative time, and complication rates. While blood loss and operative time were increased, the complication rate was not. The lower complication rate was not due to a difference in technique. The same degree of caution was applied in all cases regardless of anesthetic technique. It was this careful approach that avoided inadvertent trauma to surrounding neurovascular structures, rather than the ability of our patients to relate increased discomfort. Lamina papyracea injury was uncommon and occurred with nearly equal frequency in both anesthetic settings.

Our preference is to perform endoscopic sinus surgery under local anesthesia with sedation. This approach is associated with minimal blood loss and shorter operative time. The key to local anesthesia is threefold: 1) the skill of the surgeon in providing for meticulous surgical technique, 2) the skill and experience of the anesthetist in titrating the degree of sedation, and 3) the ability of the patient to cooperate intraoperatively. It is the responsibility of the surgeon to consider these three factors in the selection of the most appropriate anesthetic technique. An anesthetist who is not familiar with this type of surgery or not skilled in titrating appropriate sedation will likely add to the difficulty and danger of surgery. Anxious patients who are unable to cooperate or are suboptimally sedated because of medical problems or the discomfort of more extensive procedures are best given general anesthesia. Patient discomfort may lead to excessive movement or blood pressure fluctuations with excessive bleeding. Excessive bleeding and coughing may result in the reluctance of the anesthetist to provide deep sedation for fear of aspiration or, conversely, may result in oversedation and the need for resuscitation. These frustrating situations may tempt the inexperienced operator to abandon the tenets of safety presented above by hastening the dissection and risking the development of unnecessary or severe complications. In this situation the surgeon would be well advised to either prematurely terminate the procedure or consider an intraoperative switch to general anesthesia. In our series, 15 patients were switched intraoperatively and 6 operations were prematurely terminated.

We believe that there is a group of patients who will require general anesthesia, and this retrospective review of 401 ethmoidectomies documents that blood loss and operative complications can be kept to an acceptable minimum by following strict observation of specific guidelines and meticulous surgical technique. The additional blood loss and increased operative time associated with general anesthesia are acceptable if the surgeon believes this technique is preferable in specific surgical settings.

CONCLUSION

Functional endoscopic sinus surgery is a permanent addition to our specialty's surgical armamentarium. The use of endoscopes enhances the capabilities of otolaryngologists who are already experienced in sinus surgery. Experience shows that no one surgical or anesthetic technique is appropriate for every case. General anesthesia is a viable alternative for endoscopic sinus surgery. The blood loss and surgical complications can be kept to a minimum by following the strict guidelines presented above and using meticulous surgical technique.

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AERODYNAMIC ASSESSMENT OF THE SPEECH OF ADULTS UNDERGOING MULTICHANNEL COCHLEAR IMPLANTATION

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This investigation was designed to evaluate the aerodynamic characteristics of the speech of adult multichannel cochlear implant (Nucleus, 21-channel) recipients. Five adults with an acquired profound sensorineural hearing loss were tested before implantation, immediately following implantation, and 3, 6, 9, and 12 months after implantation. A commercially available computerized pressure-flow instrumentation system was employed to assess the respiratory, laryngeal, velopharyngeal, and oral articulatory subsystems of speech of the implantees. The results of the investigation indicated 1) a slight increase in airflow rate values for sustained vowel /a/ phonation after implantation, 2) a slight increase in duration of sustained vowel phonation from the preimplant period to the last postimplant period, 3) an increase in laryngeal airway resistance after implantation that resulted from a larger increase in estimated transglottal pressure than in transglottal airflow, 4) maintenance of normal velopharyngeal closure in oral-nasal contrastive contexts, and 5) slight increases in oral orifice area for fricative syllable utterances following implantation. Individual strategies for coordinated control of the speech mechanism appear to be potent variables to consider when assessing speech production.

KEY WORDS — aerodynamics, cochlear implant, deafness, speech production.

Research concerning the effects of cochlear implantation on hearing-impaired adults has concentrated primarily on aspects of speech reception and perception. The reason for this focus relates to the possibility for enhancement of the auditory input channel for receiving oral communication.

In contrast, the alterations in speech production of adventitiously hearing-impaired individuals fitted with a cochlear implant have only recently begun to receive more direct attention. The primary reason for this lack of research productivity seems to relate to the controversy that still exists concerning whether disordered speech is an identifiable and communicatively significant factor if the hearing loss is acquired after speech control is well established.[1,2]

Nonetheless, there is some evidence to suggest that postlingually deafened individuals who are implanted with single- or multiple-channel cochlear devices show improvement in speech output characteristics. The most notable changes that have been identified include regularity of vocal fold vibrations,[3] syllable fundamental frequency,[4-6] vocal intensity,[6] temporal aspects of contrastive syllable stress elements,[6,7] and articulation proficiency.[8] That is, many of the investigations cited above have noted aperiodic vibrations of the vocal folds that may contribute to perceived roughness of the voice. In addition, vocal frequency is often reported to be variable, and voice abnormally produced in a higher than normal range (high-pitched) and with vocal intensity that is too loud, too soft, and/or variable in loudness. In addition, the postlingually deafened subjects show difficulties producing appropriate stress (changes in pitch, loudness, duration) on parts of speech to be emphasized (eg, OBject versus obJECT). Finally, inability to monitor vocal output in these subjects may cause articulation to be imprecise and particular sounds such as fricatives (s in see) and affricatives (ch in church) to become distorted, slurred, and difficult to understand. These features all lead to a general degradation in overall speech understandability.

Most of the studies reported to date have dealt primarily with acoustic-perceptual characteristics of speech production following cochlear implantation. Few data are available concerning the possible aeromechanical changes in the respiratory, laryngeal, velopharyngeal (VP), and oral articulatory subsystems supporting speech following cochlear implantation. Evaluation of each subsystem serving speech production by means of aeromechanical analysis has been shown to be effective in describing subtle changes in respiratory,[9] laryngeal,[8] VP,[10] and articulatory functions[11,12] in hearing-impaired individuals and in other groups of speech-disabled individuals.[13,14] However, there are few data describing the changes in the aerodynamics of speech with a multichannel cochlear implant. Such information would seem important in describing the effects of the im-

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plantable aid on control strategies for each component of the speech-producing mechanism.

Changes in speech production may be expected if components of audition are augmented with the use of a multichannel cochlear implantation device. Recently, use of a multichannel device (Nucleus Mini-22, Cochlear Corp) has been recommended, since this device allows for stimulation of the cochlea with acoustic signals that are coded for vocal frequency, amplitude, and frequency of vocal tract resonances.[15,16] Added information about activation and cessation of voicing, and movements of the tongue, lips, velum, and jaw as determined by amplitude and frequency information about vocal tract configurations may alter the physiologic characteristics of speech produced.

Since control of speech may be enhanced in terms of intensity and frequency (vocal volume and pitch), timing (duration of speech elements), and constriction of the articulators (precision of articulation) through the use of a multichannel cochlear implant, improvement in the ability to respond to external or internal sound stimuli may be expected to influence control of aeromechanical elements of speech.

Therefore, the present investigation was designed to determine if the implantation of a Nucleus Mini-22 cochlear device would alter aerodynamic characteristics of speech performance of several subsystems (laryngeal, VP, and oral articulatory) of profoundly hearing-impaired adults examined over a 1-year period.

METHODS

Subjects. Six subjects (three women and three men) ranging in age from 27 years to 64 years, with a mean age of 39 years, volunteered for the investigation. They had a profound bilateral sensorineural hearing loss for 8 years to 30 years prior to fitting of the device. Each was tested auditorily and visually according to a predetermined protocol[17] and fitted with a Nucleus Mini-22 cochlear implant device. Each was seen for testing 2 weeks before implantation (prestimulation), within 2 weeks following the initial stimulation, and 3 months, 6 months, 9 months, and 1 year after stimulation. (See Appendix[17] for demographic data concerning each individual.)

Implant Device. The Nucleus Mini-22 cochlear implant device was implanted in each of the patients. In all cases, the 22 electrodes were inserted into the cochleae of the recipients at the time of surgery. The implant is a feature extraction device designed to provide information about the frequency of vocal fold vibration and resonances of the vocal tract through biphasic pulsatile stimulation of the 22 electrodes implanted into the scala tympani. The frequency of voicing is coded as the frequency of the pulses, and the amplitudes and frequencies of the resonances of the vocal tract (formants) are coded as amplitude and position of stimulation in the cochlea (A. Boothroyd, personal communication, 1988).

Instrumentation for Assessment. Aeromechanical assessment was accomplished with a rigid-walled vinyl pitot tube (1.0 mm inside diameter) with the proximal end situated behind the lower incisor at right angles to the first bicuspid. The distal end of the tube was joined in series to a differential pressure transducer (Statham model 113) low-pass-filtered at 150 Hz (Krohn-Hite model 3202) and transmitted to one channel of an analog to digital converter. The signal was digitized at 330 samples per second and displayed on the terminal of a Zenith model 158 microcomputer with a commercial software package (RC Electronics, ISC-16, Computerscope-Phy).

Oral (and nasal) airflow was collected simultaneously with oral air pressure. Airflow was directed from the custom-designed mask (oral or nasal) to a pneumotachograph (Sanborn model A-959) with an associated differential pressure transducer (Statham model PM15E). The output was amplified (Honeywell Accudata model 143), low-pass-filtered at 150 Hz (Krohn-Hite model 3202), and fed to another channel of the analog to digital converter and then filtered and sampled at 330 samples per second. The resultant output was then displayed on a second channel of the computer terminal with the Computerscope software package.

Calibration of the aerodynamic instrumentation was accomplished by using a U-tube manometer for pressure and a rotameter and associated tank of compressed air for flow measures. The calibration factors were used to develop measures of differential air pressure and airflow for later analysis.

Acoustic speech signals were also collected with a research-quality Bruel & Kjaer model 2608 microphone-amplifier system, and the resultant signal was fed to a third channel of the computer terminal with the Computerscope software to note duration of phonation and onset and offset of voicing.

Procedure. Each subject was seated comfortably in front of the instrumental array, and the mask and pressure sensing tube were positioned to allow for collection of the aerodynamic data by the specified speech protocol.

The stimuli in the protocol were designed to assess the laryngeal, VP, and oral articulatory subsystems. They included the following material: 1) sustaining the vowel /a/; 2) repetition of the /pi/ syllable; 3) repetition of the /isi/ syllable; 4) repetition of the sentence "The man is sad and mean"; and 5) repetition of the syllables /sis, sas, sus/ and /ziz, zaz, zuz/. Sustained vowels (/a/) provide information about respiratory control (a maximum phonation time [MPT] task using a maximum phonation volume of air — not unlike a vital capacity task) and glottal efficiency (a "leaky" glottis would provide high volume velocity airflow and, subsequently, reduced MPT values). Repetition of the syllable /pi/ has been used in other aeromechanical studies[18] to estimate transglottal pressure (instantaneous air pressure at moment of closure for /p/) and airflow on the following vowel to indicate the transglottal airflow. The ratio of the two parameters (pressure divided by flow) gives an estimate of glottal resistance — not unlike the electrical formula for resistance (Ohm's law): R = E/I. Production of the syllable /isi/ and the sentence "The man is sad and mean" is designed to provide contexts in which the firmness of VP closure is challenged by employing a high vowel /i/ and a continuant consonant /s/, which demands closure to remain "oral" in production characteristics. The sentence has nasal consonants surrounding oral sounds (is sad) to force the VP system to open and close quickly in order to produce oralization in an environment of nasal sounds. Oral articulatory precision is best assessed by challenging the oral articulators to form a tight constriction (precise articulation) employing the /s/ and /z/ sounds, which are the same in place of production, but differ in voicing. In most cases, consonant elements were the subject of analysis, since they provide the most easily measured and most useful sound element to provide information about the efficiency of each valve (ie, VP) within the speech subsystems.

Each subject repeated each of the stimuli, as displayed in graphic form, three times (eg, /isi, isi, isi/) in a predetermined (randomized) order at each of the six testing periods (prestimulation, 6 months poststimulation, etc). If there were difficulties in repetitions of the tasks as presented graphically, the stimuli were presented again until the requisite number of test items were available for analysis. The resultant data were then stored on a computer disk for later descriptive and statistical analysis.

Measurement Methods. Measures of oral air pressure were made by placing one of the computer programs' cursors on the pressure peak for the appropriate consonant element (eg, /p/ in /ipi/) and moving a second cursor to intersect the flow trace that was displayed simultaneously on another channel of the terminal-Computerscope screen. These pressure-flow values served as data for computation of orifice area (either VP or oral).[19] The pressure-flow values were placed into a computer program for calculation of orifice area by the following equation:

$$(1) \qquad OA = \mathring{V}/k\sqrt{\frac{2\Delta P}{d}}$$

where OA is the area of the orifice in square millimeters, $\mathring{V}$ is the nasal (or oral) airflow in milliliters per second, d is the density of air (0.001 g/cm^2), ΔP is the pressure drop across the orifice in dynes per square centimeter, and k is the discharge coefficient (0.65).

For the laryngeal airway resistance (Rlaw) measures, Ohm's law for electrical circuits was modified[13] to evaluate aerodynamic values. The result was that Rlaw was calculated by taking the midpoints of the middle three of seven intraoral pressure traces for the repetitions of the syllable /pi/ with one cursor and determining the airflow value by placing another cursor vertically from the pressure trace to the corresponding airflow trace on the Computerscope. The resultant pressure-flow values were placed into the following formula:

$$(2) \qquad Rlaw = \Delta P/\mathring{V}$$

where ΔP is the differential transglottal air pressure in centimeters of water, $\mathring{V}$ is the transglottal airflow in cubic centimeters per second, and Rlaw is the laryngeal airway resistance in centimeters of water per liter per second.

Average volume velocity airflow during sustained vowel /a/ productions was measured by moving cursors along the airflow trace and averaging the converted voltage values to airflow reported in cubic centimeters per second. Duration of the sustained phonation was calculated by taking the total duration (in milliseconds) from the beginning of the voicing trace to the end of phonation. All of the pressure-flow and temporal data were stored on a computer disk and used for the later statistical analyses.

Interjudge and intrajudge reliability was determined by remeasurement of 5% of the test stimuli. Intrajudge reliability was determined to be quite high (r = .98), and interjudge reliability was also high (r = .93).

RESULTS

In order to evaluate the effects of the implant on the speech of our subjects, the data were examined from the laryngeal mechanism "upstream" to the oral articulators. The results obtained were plotted as percent improvement scores. The percent improvement score was the difference between the score obtained during a given assessment period for a given parameter (eg, duration of MPT at 6 months poststimula-

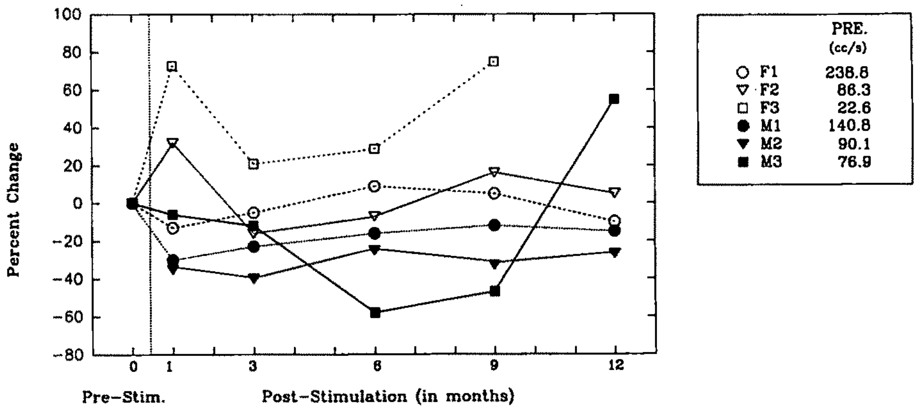


Fig 1. Percent change for transglottal airflow rate during sustained vowel /a/ production (values in cubic centimeters per second).

tion) and the score obtained during the prestimulation assessment session. (The actual prestimulation assessment scores are reported in the Figure keys.) Each individual's data for each parameter are plotted with coded symbols used to display changes over time. In addition to the visual description of the changes in each parameter (as a positive or negative sign to show an increase or decrease from the prestimulation value), the sign test[20] is provided to note significant changes from zero for each assessment test for each time period.

The data displayed in Fig 1 show percent change of transglottal airflow during production of the sustained vowel /a/ for the six subjects. On average, there is a gradual decrement for five of the six individuals in mean airflow rate for sustained vowel /a/ from the prestimulation period to 6 to 9 months poststimulation. Two of the male subjects (M1 and M2) showed significant changes (p = .03) from prestimulation values over the 1-year period. One female subject (F3) increased from prestimulation to poststimulation values, but visualization of her values for low transglottal airflow rates at the beginning of the assessment suggests that she was moving toward a more normal range of airflow values (ie, 90 to 120 cc/s). Similarly, subject M3 started at the low end of normal airflow rate, decreased after stimulation, and returned to more normal levels by 1 year poststimulation.

The data displayed in Fig 2 show percent changes in duration of the MPT task for sustained production of the vowel /a/. In general, there is a numeric increase in MPT values for four of the six subjects from prestimulation to 1 year poststimulation. None of the subjects showed significant changes from prestimulation times over the whole year. Two subjects (F1 and M1) showed a slight decrease at the 1-year assessment period, but had displayed greater than prestimulation values in MPT up to the 9-month period. The sign test showed that the most significant positive changes (p = .02) in MPT for each of the subjects occurred at the 6-month poststimulation period.

Since part of the study was designed to note the relationship between the driving respiratory subglottal pressure and the transglottal airflow as a method to estimate laryngeal airway resistance, an assessment of the Rlaw component of each subject's voice was completed by using a modification of Ohm's law for aerodynamic activity. The data displayed in Fig 3 indicate that laryngeal airway resistance increased numerically from prestimulation to 9 months to 1 year poststimulation. Subjects F1 and M1 showed significant positive changes (p = .03) over the entire period. As a group, the subjects showed most positive changes between 6 and 9 months poststimulation.

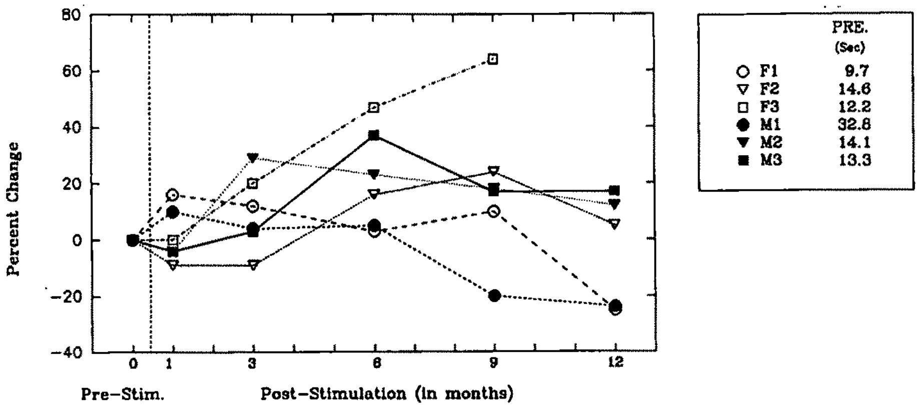


Fig 2. Percent change in duration of maximum phonation time during sustained vowel /a/ production (values in seconds).

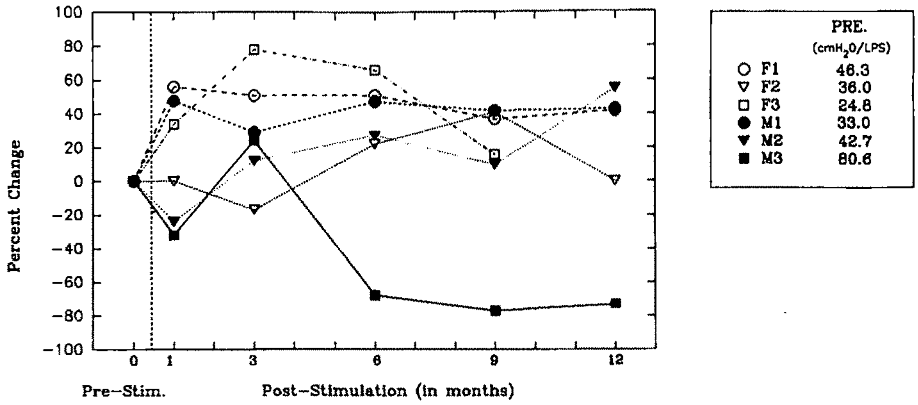


Fig 3. Percent change in laryngeal airway resistance during syllable /pi/ repetition (values in centimeters of water per liter per second).

Only one subject (M3) showed a major decrement in laryngeal airway resistance from the third month to the 1-year poststimulation assessment period, and his values before implantation were more than twice the values normally expected. Since the Rlaw values became greater for most patients from prestimulation to poststimulation, it was of interest to note what strategies were used to alter laryngeal resistance following implantation.

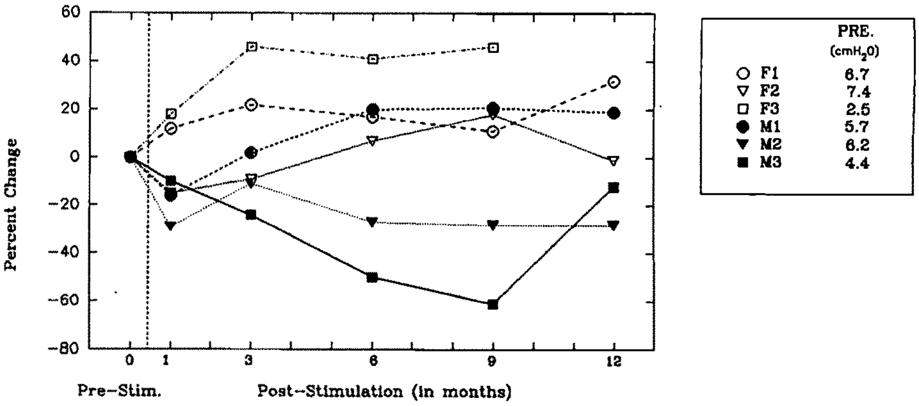
Since there was such an increase in Rlaw values from prestimulation to poststimulation test periods, data representing pressure and flow values are presented to demonstrate the aerodynamic strategies used to generate these values. The data in Fig 4 indicate that four of the six subjects increased transglottal air pressure, two of them (F1 and F3) significantly ($p = .03$ and $p = .06$), from pretesting to 9 months poststimulation. Two subjects (M2 and M3) decreased air pressure values significantly ($p = .03$) immediately poststimulation and maintained these lower values across the poststimulation test periods. Again, the largest changes for the subjects as a group occurred between 6 and 9 months poststimulation.

Review of the data for airflow rate during this airway resistance task (Fig 5) shows that airflow rate decreased numerically from prestimulation to poststimulation periods. Four of the six subjects had numerically decreased airflow rates, and those of three of the subjects (F1, M1, and M2) decreased significantly ($p = .03$) over the 1-year period from prestimulation tests. One subject (M3) increased airflow significantly ($p = .03$) from prestimulation to 1-year poststimulation testing. The greatest decrease in transglottal airflow occurred between the third and sixth month poststimulation.

Measures of the VP port size assessed aeromechanically may be seen in Fig 6. By using the equation for estimating orifice area[19] described previously, the pressure and flow data associated with the oral consonants in the syllable /isi/ and sentential context ("The man is sad and mean") were converted to estimates of VP orifice size.

The data in Fig 6 show that the subjects in this study had estimated VP orifice areas of less than 4 mm^2 (0 to 5 mm^2 is within normal limits) during both syllable /isi/ repetition and for assessment of VP opening during oral consonant production within a sentence context for prestimulation and all poststimulation assessment times. Three of the subjects (F2, F3, and M2) showed significant decreases in VP orifice over time. The most significant changes for the subjects, as a group, were at the 1-year test period. There were very small numeric changes across testing time periods for these measures, with values for the simple syllable context (/isi/) being smaller (ie,

Fig 4. Percent change in transglottal air pressure associated with laryngeal airway resistance measures during syllable /pi/ repetition (values in centimeters of water).



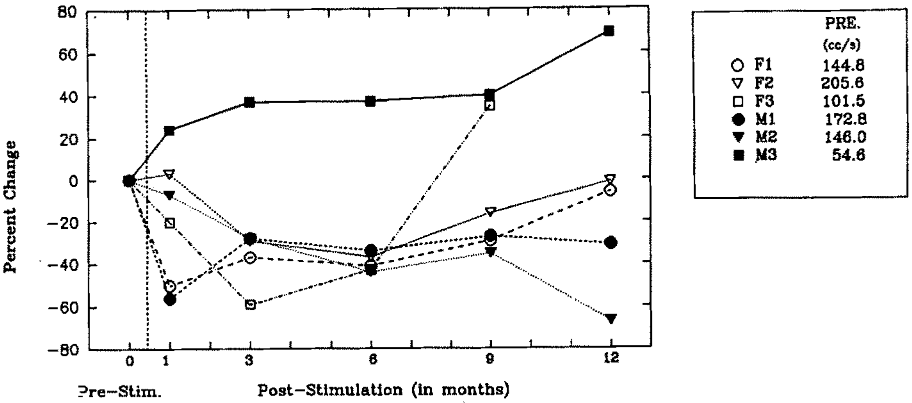


Fig 5. Percent change in transglottal airflow associated with laryngeal airway resistance measures during syllable /pi/ repetition (values in cubic centimeters per second).

more close constriction of VP closure) than for the sentence context ("The man is sad and mean"), which included some nasal consonants. As with the syllable context, the VP orifice areas for the sentence passage were all within normal limits (less than 4 mm^2). Two of the subjects (F3 and M2) who demonstrated significant reduction in the syllable context showed significant decreases in VP area in the sentence context from prestimulation to poststimulation test periods.

Figure 7 shows the size of oral port constriction estimated from pressure-flow measures by using the Warren and DuBois[19] orifice area equation made during fricative /s/ consonant production within a consonant-vowel-consonant context (ie, /sis, sas, sus/). The data in the Figure show that three of the subjects (F1, F2, and M3) had increased (more open) oral orifice areas, while three (F3, M1, and M2) had decreased oral orifice areas for syllable /s/ productions. Four of the subjects (F1, F2, F3, and M1) showed significant changes ($p = .03$ to $p = .06$) in oral port constriction from prestimulation to poststimulation assessment times. A visualization of the data indicates that subjects either increased or decreased in oral orifice area immediately after stimulation and then maintained that strategy across the 1-year time frame.

As with the voiceless /s/ consonant syllables, the /z/ phoneme contexts (/ziz, zaz, zuz/; Fig 8) showed that three subjects (F1, F2, and M3) numerically increased oral port size across testing periods — one significantly (F1; $p = .03$) — while three (F3, M1, and M2) numerically decreased oral port size — two significantly (F3 and M2; $p = .03$) — from prestimulation to 1 year poststimulation. Subjects showed their greatest change at the 3-month poststimulation period. In general, orifice sizes were slightly smaller numerically for voiced /z/ contexts than for voiceless /s/ contexts.

In general, intraoral air pressure underlying production of the oral orifice equation for /s/ showed increases for three of the six subjects across time, with four of the six subjects showing a decrease in oral airflow from prestimulation to poststimulation periods. As with other measures, most subjects chose a strategy of increasing or decreasing pressure or flow following stimulation and maintained it throughout the testing period. A similar pattern was observed for pressure and flow patterns for the six subjects during production of the /z/ syllables. That is, half chose to increase, and half to decrease pressure and/or flow from prestimulation levels to 1 year poststimulation.

DISCUSSION

This study was designed to evaluate the aeromechanical changes that occurred at each of the valves

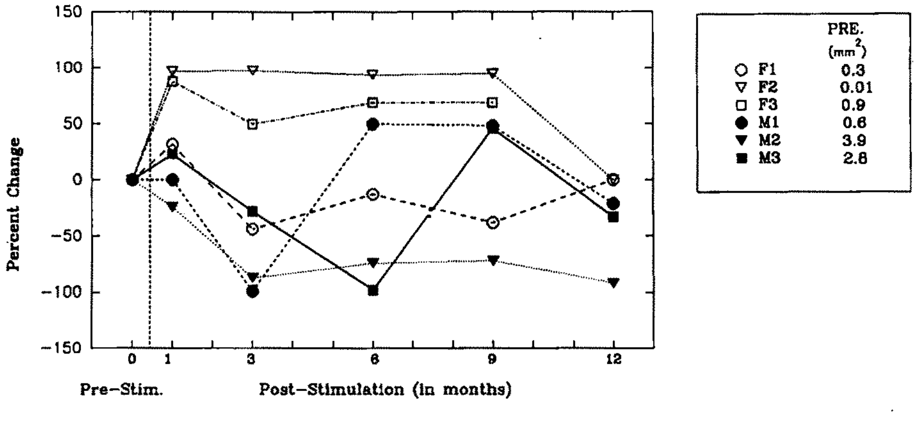


Fig 6. Percent change in velopharyngeal orifice area during syllable /isi/ production (values in square millimeters).

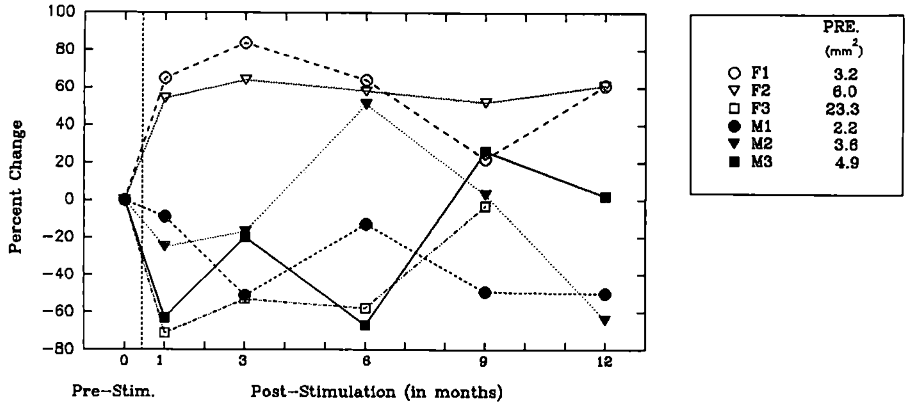


Fig 7. Percent change in oral air pressure associated with oral port constriction (size) measures during syllable (s-vowel-s) production (values in square millimeters).

(laryngeal, VP, and oral articulatory) regulating speech after the subject received a multichannel cochlear implant. The results of this study demonstrated improved aeromechanical efficiency of several valves (laryngeal and oral articulatory) within the speech subsystem. It is also important to note that each of the subjects appeared to have a unique strategy for regulating the pressure-flow characteristics of speech production following implantation.

In particular, the results indicated that the regulatory mechanisms for the laryngeal subsystem showed increasing changes through 6 to 9 months poststimulation. The increases in MPT of the vowel /a/ poststimulation are supported by the finding that transglottal airflow rate decreased for four of the six subjects. This suggests that a major strategy for increasing glottal efficiency for a majority of subjects is decreasing flow rate, hence improving the duration of phonation. Support for changes in speech breathing following multichannel cochlear implantation may be seen in a recent investigation with postlingually deafened adults.[21] Further support for individual strategies for regulation of aerodynamics at the level of the laryngeal mechanism comes from the Rlaw data. For five of the six subjects, Rlaw increased from prestimulation levels. Since Rlaw is a ratio of air pressure to flow, a review of the estimated transglottal pressure and transglottal airflow suggests that four of six subjects reduce airflow and increase air pressure to "improve" their glottal efficiency.[18] It is interesting to note that the airflow values during the sustained /a/ MPT task are consistent with those determined for the Rlaw task. Such adjustments may relate to the subjects' attention to the voicing component as enhanced by the frequency pulse information from the mini speech processor unit. Adjustments of the voicing system via feedback from other auditory or implant hearing devices have been reported in the literature[4,6,22] (also A. Boothroyd, personal communication, 1988). In general, other researchers have found that there are positive changes in stabilization of vocal frequency and intensity and increased speaking rate following cochlear implantation.[4,6]

Contrary to the changes demonstrated for the laryngeal subsystem, the VP system showed very little change following implantation. As such, the orifice area values (less than 4 mm^2) were all "within normal limits"[13,14] as noted for normal-hearing speakers. In addition, while the percent change in VP closure shows some variability in VP action for both simple syllables and sentence contexts, the changes were usually less than 1 mm^2. Thus, it appears that the VP subsystem in adventitiously hearing-impaired individuals maintains appropriate opening and closing gestures during coarticulatory speech events. This finding supports a hypothesis of an overlearned mo-

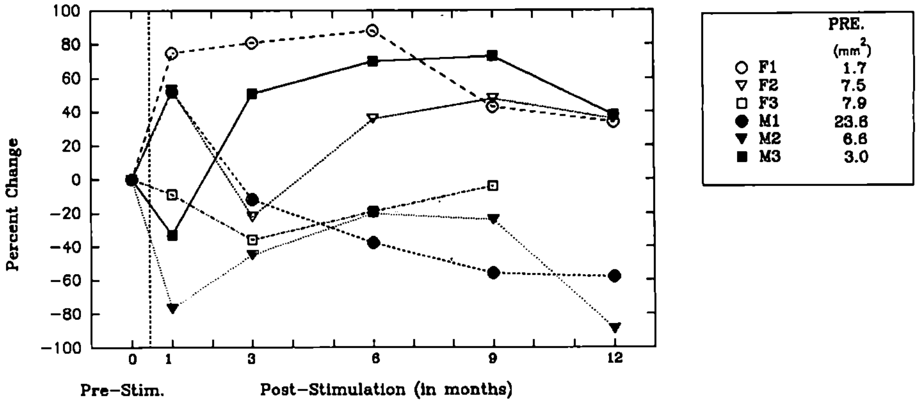


Fig 8. Percent change in oral airflow associated with oral port constriction (size) measures during syllable (z-vowel-z) production (values in square millimeters).

tor patterning control system that does not break down as rapidly as other subsystems.[19,22,23]

A review of the oral articulatory subsystem shows that a majority of implanted subjects increased the oral constriction (had more closed articulatory gestures) for the s-vowel-s syllables, while several decreased constriction (as noted by increased oral port constriction — more open gestures) over the 1-year assessment period. The acoustic and perceptual consequences of a more constricted oral port are for hearing-impaired subjects to substitute a "stop" phoneme (eg, /t/) for a continuant sound (eg, /s/), ie, tet for set. Other hearing-impaired subjects may produce a "slushy" phoneme representation of a fricative sound (ie, sheet for seat). Such descriptions of articulation have been provided by other investigators.[7,8,24] Realization of the changes in oral port constriction and the underlying pressure-flow relationships may help the speech clinician in dealing with techniques of alteration of either the overarticulation or underarticulation of certain speech sounds that are difficult to monitor for hearing-impaired speakers. Certainly, speech clinicians should be encouraged to use aerodynamic evaluations to evaluate the valves within the speech system, since the methods may be used for fine assessment[11] of the speech valves, as well as for therapeutic biofeedback. Further, these methods are both noninvasive and nonintrusive and may be used within a variety of speech therapy programs to determine which valve(s) is either hyperfunctional or hypofunctional.

The results of the present study must be viewed with caution and within the context of assessment and management with a cochlear implant without the benefit of behavioral treatment (speech therapy). Hence, the design of the present study did not allow for a multiple-baseline treatment analysis. Thus, it is not possible to determine which components of the aeromechanical changes may be related to auditory enhancement by the implant and how much is related to the subjects' reliance on aerodynamic feedback.[23] Further research is currently under way to evaluate the effects of auditory and/or tactile-kinesthetic feedback by using a staggered multiple-baseline repeated single-subject design including speech therapy techniques.

While the results of the present investigation are encouraging, the effects of restoring the auditory feedback channel with a multichannel implant must be thoroughly evaluated. It may be that the multichannel device provides more information on the frequency, frequency transitions, and frequency-intensity patterning of speech that is useful for altering articulatory activities at several of the subsystems serving speech. More extensive research is needed with persons undergoing multichannel cochlear implants to determine individual strategies for interarticulator timing.[12] The degree to which aeromechanical features of speech production may be incorporated in training programs should also be explored.[8,25] Finally, rate of change in learning control at each of the subsystems demands more detailed study employing a larger number of subjects subgrouped for a variety of sensory, motor, and communication factors that may affect speech production.

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APPENDIX

DESCRIPTIONS OF CAUSE AND TYPE OF HEARING LOSS, TIME SINCE ONSET OF LOSS, AGE AT IMPLANTATION, SPEECH PROCESSOR AND MODE OF OPERATION, AND GENERAL SPEECH CLASSIFICATIONS FOR SUBJECTS EXAMINED IN PRESENT STUDY

The first four subjects examined in this study were previously described in detail elsewhere.[17] Subject F1 (subject KF in Gagné et al[17]) had speech performance classified as moderately impaired; subject F2 (subject AR), mildly impaired; subject M1 (subject RO), moderately impaired; and subject M2 (subject JC), mildly impaired.

There were two additional subjects for the present study. Subject F3 was a woman, 52 years of age on her day of surgery. The cause of the loss is unknown; however, there was a positive family history of progressive sensorineural hearing loss. The onset was in childhood, and she had had a profound hearing loss for the past 10 years. She had worn a body-type hearing aid until the implant surgery. The pure tone average (PTA) in the better ear unaided was 110 dB hearing level (HL) and the PTA for the better ear aided was 60 dB HL. The patient was fitted with a mini speech processor programed in a bipolar plus one stimulation mode. Her speech performance was classified as mildly impaired.

Subject M3 was a man, 40 years of age on his day of surgery. The cause of the loss is unconfirmed, but a viral infection is suspected. The onset was at approximately 10 years of age, and the duration of the profound loss was 30 years. The patient had not worn a hearing aid for the last 30 years. The PTA in the better ear unaided was 115 dB HL at 500 Hz, and there was no response at 1 or 2 kHz. The PTA in the better ear aided was 100 dB HL at 500 Hz, and there was no response at 1 or 2 kHz. The subject wore a mini speech processor that was programed in the bipolar plus two stimulation mode. His speech performance was classified as severely impaired.

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ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA (HISTIOCYTOID HEMANGIOMA): EVALUATION OF TREATMENT OPTIONS

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Angiolymphoid hyperplasia with eosinophilia is an uncommon benign vascular proliferative lesion of unknown cause. In this report, a case is presented of a patient who was confirmed to be positive for human immunodeficiency virus and in whom the lesion had shown rapid accelerated growth. The case is used to illustrate a variety of therapeutic techniques and to evaluate the effectiveness of the various alternatives in the treatment of this unusual clinical problem. Long-term follow-up after radical excision of the tumor mass is presented.

KEY WORDS — angiolymphoid hyperplasia, histiocytoid hemangioma, temporoparietal fascial flap.

INTRODUCTION

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon benign vascular proliferative lesion of unknown cause. Also called histiocytoid hemangioma, the lesions present clinically as vascular skin nodules of various sizes and shapes in the head and neck region, affecting the skin and subcutaneous tissue. The cause of this disease remains unknown, and physicians have used a variety of treatment modalities including cryosurgery, intralesional steroid injections, electrodesiccation, curettage, radiotherapy, laser therapy, and excision.[1]

CASE REPORT

A 24-year-old woman presented to the Massachusetts Eye and Ear Infirmary with an 8-year history of multiple slowly growing vascular lesions of the scalp and auricular area. A single right auricular mass had shown accelerated growth in the months preceding this admission. In addition, new lesions had appeared, gradually involving the right preauricular area, the right side of the scalp, and the forehead. The masses were intermittently pruritic, and 3 to 5 days prior to admission the masses had become painful and purulent. She presented to the Massachusetts Eye and Ear Infirmary emergency room after developing a fever of 40°C.

Her medical history was remarkable for a 1 to 2 pack per day smoking history, use of intranasal cocaine, and a heterosexual relationship with an intravenous drug user. She denied any intravenous drug use.

Physical examination revealed multiple vascular masses of the right ear and scalp (Fig 1), with an area of auricular and scalp cellulitis. The masses were firmly compressible and ranged in size from 3 mm to 3 cm. Alopecia of the right temporoparietal scalp was present, extending in a zone around most of the scalp lesions. Neck examination revealed extensive nontender lymphadenopathy of both anterior cervical triangles. The remainder of her physical examination revealed an excoriated papular rash on her arms, legs, and back consistent with eczematous dermatitis. Laboratory studies revealed a hematocrit of 31, a white blood cell count of 5.5 with 8% eosinophils, and a sedimentation rate of 44. A computed tomography scan confirmed the presence of extensive cervical lymphadenopathy.

Within 48 hours, the regional cellulitis responded to intravenous nafcillin sodium and clindamycin phosphate. Cultures subsequently grew rare diphtheroids, rare coagulase-negative staphylococci, and a few anaerobic gram-positive cocci. Biopsy of the auricular lesion yielded a diagnosis of ALHE. The areas of alopecia showed follicular mucinosis.

The patient had a test for human immunodeficiency virus (HIV), which was positive (enzyme-linked immunosorbent assay and Western blot). Cervical lymph node biopsy revealed only chronic inflammation.

Treatment. A review of the literature revealed no clear consensus on optimal treatment.[2-12] Conse-

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From the Department of Otolaryngology (Cheney, Bhatt) and the Medical Unit (Hibberd), Massachusetts Eye and Ear Infirmary, the Department of Otolaryngology, Harvard Medical School (Cheney, Bhatt), and the Infectious Disease Unit, Massachusetts General Hospital (Hibberd), Boston, Massachusetts; and the Department of Pathology, University of Tennessee Medical Center at Knoxville, Knoxville, Tennessee (Googe).

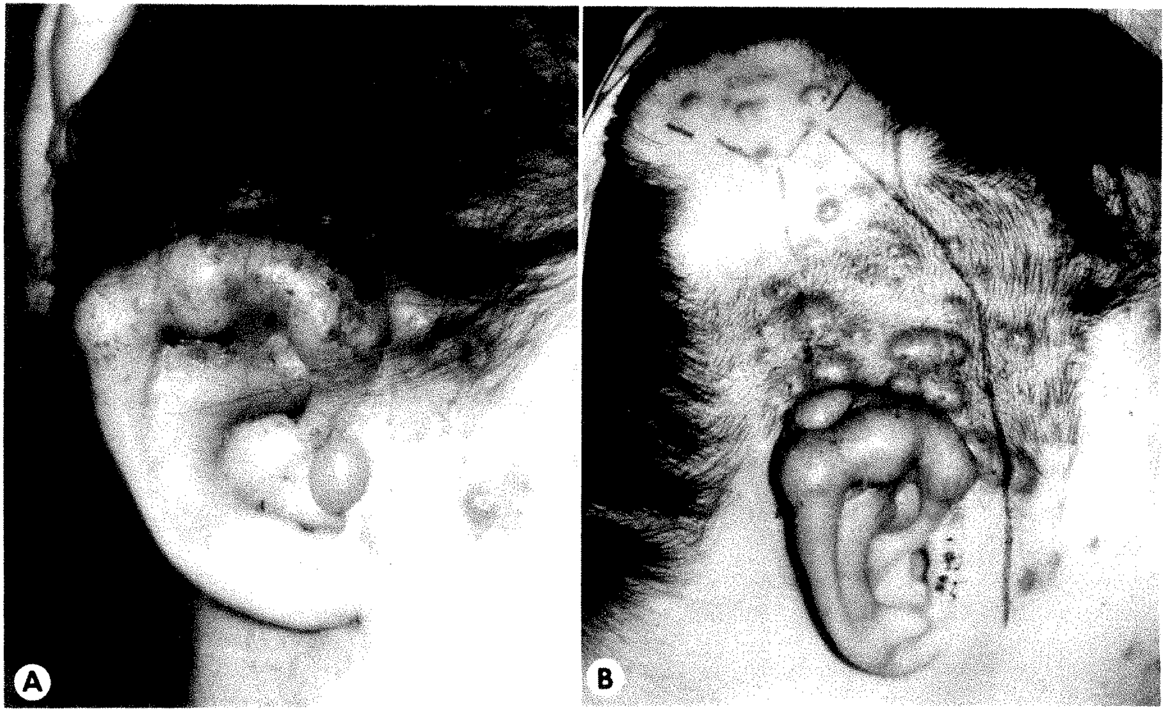

Fig 1. Auricular and periauricular lesions. A) Preoperative. B) With demarcation of proposed surgical incision site.

quently, with the patient's consent, a variety of therapies were applied to her multiple lesions. Smaller lesions received intralesional steroids (Kenalog), carbon dioxide (CO_2) laser vaporization, argon laser treatment, or cryosurgery using multiple freeze-thaw techniques.

In view of the fact that cellulitis was a recurrent and chronic problem in this patient, the decision was made to excise the lesions of the auricle with retention of the auricular cartilage. A temporoparietal fascial flap was elevated for coverage of the cartilage, and an immediate skin graft was placed (Fig 2A-C).

During the first postoperative month, lesions treated with the CO_2 laser and cryotherapy disappeared. Argon laser–treated lesions regressed moderately, and steroid-treated lesions remained unaffected. All laser-, steroid-, and cryotherapy-treated lesions recurred grossly within 6 months and were subsequently excised, with no noted return of the lesions after 4 years.

The initial CD4-positive cell count was 150, and the patient was started on a regimen of zidovudine (azidothymidine) therapy and prophylaxis against *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole. In the 24 months after presentation she took azidothymidine intermittently because her hematocrit fell to between 24 and 27 on therapy. She was unable to tolerate trimethoprim-sulfamethoxazole over the last 6 months of the second year of treatment because of a severe skin rash and was noncompliant with aerosolized pentamidine treatment. Oral hairy leukoplakia was present for approximately 4 months. The patient was treated for thrush during this same period. Despite a CD4-positive count that varied between 50 and 71, she did not develop any opportunistic infections consistent with the diagnosis of acquired immunodeficiency syndrome. She had three episodes of tracheobronchitis and pneumonia associated with *Hemophilus influenzae* that responded to therapy with ciprofloxacin hydrochloride. Vaccinations with pneumovax, influenza, and more recently *H influenzae* have been administered. With a follow-up of 4 years, the lesion that was excised to auricular cartilage has shown no evidence of recurrence (Fig 2D).

Pathologic Findings. Biopsies from the ear and scalp lesions demonstrated an extensive dermal infiltrate of lymphocytes admixed with numerous eosinophils (Fig 3A). The infiltrate was perivascular and interstitial: lymphoid follicles with germinal centers present in the dermis. The inflammatory infiltrate extended into the subcutaneous fat. Epidermal hyperplasia with spongiosis and exocytosis of lymphocytes into the epidermis were also present. An increased number of well-formed blood vessels with prominent endothelial cells were present throughout the dermis. The endothelial cells were large, with ample cytoplasms that were occasionally vacuolated (Fig 3B). Their nuclei were vesicular and often clefted or grooved.

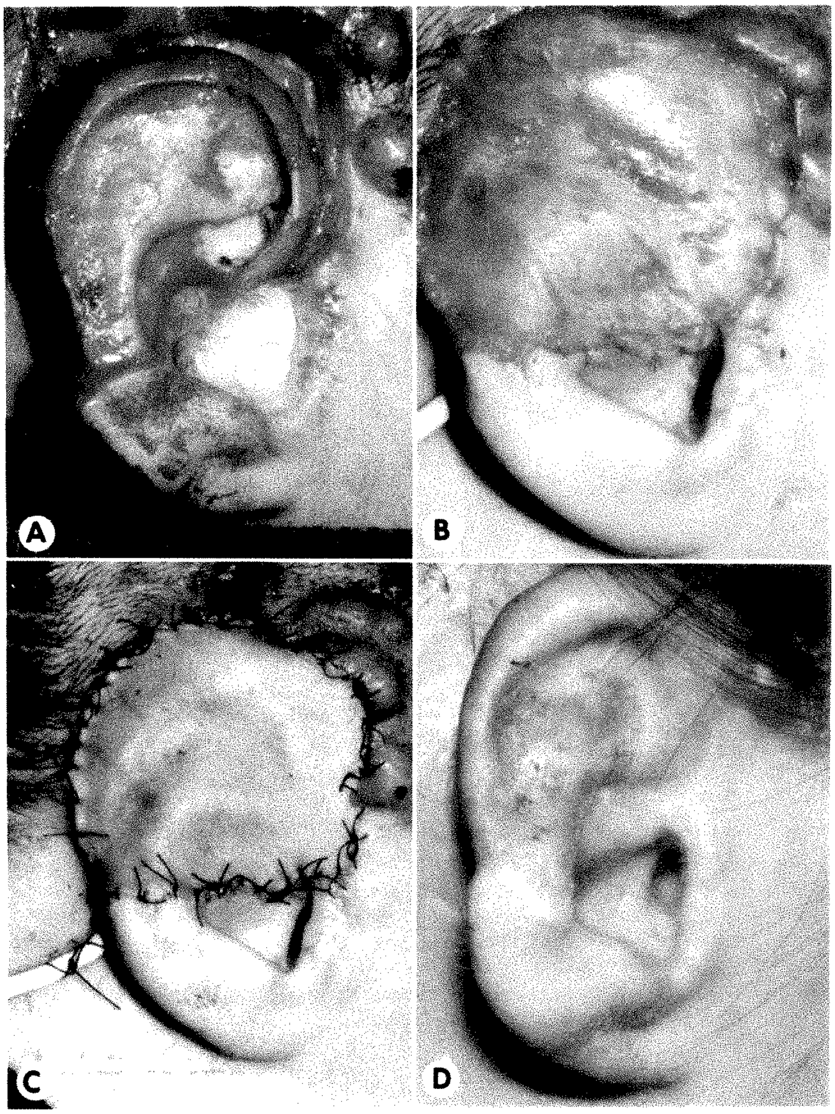

Fig 2. A-C) Surgical excision of lesions down to auricular cartilage with coverage from temporoparietal fascial flap and split thickness skin graft. D) Postoperative appearance at 4 years.

The excisional specimen from the right auricle grossly showed nodular deformation of the dermis covered by hairless skin. Prominent vessels were present in the subcutaneous fat. Microscopic examination of the auricular specimen demonstrated a marked increase in the number of well-formed blood vessels throughout the dermis and subcutaneous fat (Fig 3C). These blood vessels had thick walls and varied between 50 and 100 μm in luminal diameter. Some appeared to have smooth muscle within the media. Elastic laminae were not recognized in the superficial vessels. The endothelial cells of these vessels were large, with abundant cytoplasm that occasionally was vacuolated. The endothelial cell nuclei were large and vesicular, with prominent nuclear folds or grooves (Fig 3D). No lymphoid follicles were seen. Of interest was the extension of lymphocytes into hair follicles, with accumulation of mucin within the follicular epithelium (follicular mucinosis). No dermal scarring was apparent.

Special stains for bacteria including Warthin-Starry and Brown-Hopps stains were negative. Electron microscopy did not identify viral particles within the endothelial cells.

Microscopic examination of scalp lesions treated by cryotherapy, steroid (Kenalog) injection, and argon laser showed minimal alteration in comparison to untreated lesions. A lesion treated with a CO_2 laser showed superficial dermal fibrosis, with persistence of abnormal vessels in the deep dermis.

DISCUSSION

Angiolymphoid hyperplasia with eosinophilia is an unusual but widely discussed benign tumor of the skin. The entity was first described by Wells and Whimster[13] in nine patients with subcutaneous nodules of the head and neck region, often associated with blood eosinophilia. Since this time many reports of ALHE have emerged, further elaborating and

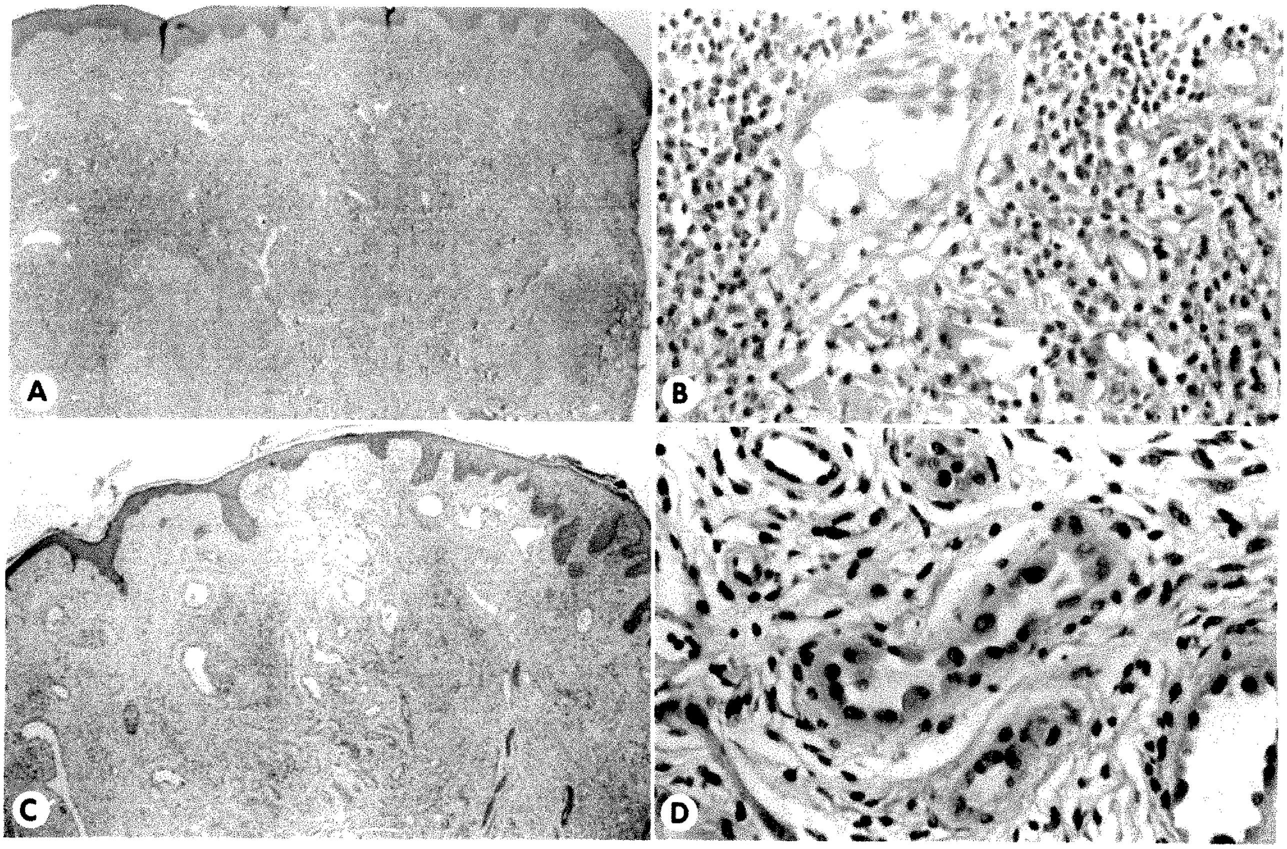

Fig 3. Pathologic findings. A) Biopsy of auricular lesion before antibiotic therapy show extensive infiltrate of lymphocytes, plasma cells, and eosinophils throughout dermis and subcutaneous fat with prominent increased vascularity (H & E, original x4). B) Before antibiotic treatment, blood vessels in dermis and subcutaneous fat of biopsy specimen are ectatic and have large endothelial cells with abundant eosinophilic cytoplasm that protrude into vascular lumens (H & E, original x20). C) Excision specimen shows persistence of increased number and size of dermal and subcutaneous blood vessels (H & E, original x4). Inflammatory infiltrate and lymphoid follicles have subsided following antibiotic treatment. D) Endothelial cells within vascular proliferation have abundant eosinophilic cytoplasm, have vesicular nuclei, and protrude into vessel lumens (H & E, original x40). Some nuclei appear grooved or folded.

defining its characteristics.

The case presented is typical of this entity. The patients present with slowly growing pink-purple nodules, usually located in the preauricular or scalp area. Seventy percent of patients are female, usually in the second to fifth decades. Nodules may be single, but are multiple in about half of the cases. The nodules are usually asymptomatic, with one fifth being pruritic and fewer still friable. The mass or masses are rubbery in consistency and appear vascular but do not blanch with pressure. Although all tumors by definition contain dense eosinophilia, only about one fifth of patients have eosinophilia of the blood. Lymphadenopathy is an uncommon finding. Alopecia is unusual in ALHE, this being only the third case reported to involve hair loss.

Many treatments for ALHE have been described in the literature, including intralesional and systemic steroids, electrodesiccation, curettage, radiotherapy, laser therapy, and excision. Steroid therapy is ineffective locally, and only transiently effective when given systemically. Electrodesiccation and curettage techniques are often followed by rapid recurrences. Radiotherapy has been quite effective in most cases; however, the risks of carcinogenesis may outweigh the benefit, particularly in the young patients who typically have ALHE. Thompson et al[11] described the CO_2 laser as effective in vaporizing an ALHE mass with no recurrence at 14 months. The majority of lesions have been treated by simple excision with narrow margins. Recurrences have been infrequent with this technique.

The lesions in this patient that were treated by nonsurgical techniques showed a variable response. The lesions treated with a CO_2 laser, cryotherapy, and argon laser showed clinical improvement but recurred. The lesion treated by steroid injection did not respond. Histologically, the lesion treated with a CO_2 laser showed dermal fibrosis, with a residual vascular lesion present beneath the scar. Posttreatment histologic examination of the other lesions showed persistence of the vascular proliferation.

The response to different treatment modalities may be predicted after studying the pattern of the vascular proliferation within lesions. There are proliferated vessels similar to small arteries, arterioles, and capillaries throughout the subcutaneous fat and dermis. These growth characteristics of ALHE are similar to those of lobular hemangioma (pyogenic granuloma), which also may have arborizing vessels that extend from superficial to deep. It is well recognized that superficial ablation of lobular hemangioma leaves a deep component that can be the source of recurrence. With this in mind, conservative, complete removal is typically required to prevent recurrence.

Ablative modalities such as the CO2 laser and surgery are effective in ALHE if the lesion is completely removed. However, treatment modalities that do not reach the deep components of these vascular proliferative lesions cannot be expected to be curative. Coagulation necrosis may be produced with a CO2 or argon laser. Tissue effects decrease with the depth of penetration, and the deep aspects of ALHE may not be as affected by these modalities.

Successful cryotherapy requires that the entire lesion be frozen for sufficient time to cause vascular injury, thrombosis, and necrosis. Predictably, achieving complete thermal damage in a vascular lesion such as ALHE would be difficult without affecting surrounding normal cutaneous structures.

Fortunately, ALHE appears to be a slow-growing, benign lesion producing a cosmetic deformity, with rare complications such as hyperrenin states and hypertension. Therefore, conservative therapy with follow-up and treatment of recurrences is acceptable. When clinically and cosmetically feasible, we recommend conservative, complete surgical excision. Pretreatment with broad-spectrum antibiotics may be helpful in reducing inflammation. In situations in which surgical extirpation is not feasible, laser coagulation should be considered. Cryotherapy seems of little use, and while steroid injections are relatively safe, they seem to have little efficacy.

The appearance of a "classic" case of ALHE is quite characteristic; however, other head and neck skin tumors may give a similar appearance. Cylindromas, or turban tumors, are multiple pink or blue nodules of the body, located most often on the scalp. Eccrine or apocrine cell in origin, these tumors have an autosomal dominant hereditary pattern and grow slowly with time. Histologically, these tumors are quite different from ALHE, being composed of epithelial cell islands rather than endothelium and neovascularization. Angiosarcoma is a malignancy that also may be present as a blue or purple mass; however, unlike ALHE, it is a continously growing and infiltrative tumor, usually involving the scalp of older patients.

Kimura's disease is an entity, often confused with ALHE, that also involves mass lesions of the head and neck.[14-17] Compared to those of ALHE, however, these lesions tend to be much larger; they are deep-seated and of long duration, with no abnormality of the overlying skin. Kimura's disease also tends to affect primarily young East Asian males and includes marked, at times massive, lymphadenopathy as a prominent feature. Early articles described ALHE and Kimura's disease as being related; however, recent analysis shows many distinctions histologically. Most important, vascular proliferation is unusual in Kimura's disease.

The importance of an accurate diagnosis of ALHE cannot be overstated. It may mimic a variety of skin neoplasms, including skin appendage tumors, pyogenic granuloma, Kaposi's sarcoma, and angiosarcoma. Careful histopathologic evaluation of biopsy material is important in directing patient care.

To our knowledge, ALHE has not been reported in an HIV-infected patient. A lesion recently described as bacillary angiomatosis, however, has been seen with regularity in HIV-infected patients. These lesions may be distinguished histopathologically by the presence of bacilli around proliferated dermal capillaries. These bacilli have similarities to the cat-scratch bacillus and *Bartonella* sp. These lesions may clear with antibiotic therapy.

The lesion of ALHE is vasoproliferative, with a variable inflammatory component. It may be multifocal, but does not show the metastatic behavior typical of malignant neoplasms. It is unclear if ALHE is a response to infection, a benign vascular neoplasm, or a component of an altered immune response.

As this is the first reported case of ALHE in an HIV-positive individual, the presence of the virus may explain some atypical features seen in this patient. Lymphadenopathy is uncommon in ALHE, but is common in patients infected with HIV. Although lymphadenopathy is frequently benign, Hodgkin's disease, non-Hodgkin's lymphoma, primary central nervous system lymphoma, and other cancers have been found in patients with HIV disease. In the HIV-infected patient, secondary viral infections are associated with several malignancies (eg, Epstein-Barr virus is associated with Burkitt's lymphoma and B cell lymphoproliferative disease), herpes simplex virus type 2 is associated with cloacogenic carcinoma of the anus, and herpes simplex virus type 1 is associated with squamous cell carcinoma of the tongue. A two-step model has been proposed to explain the development of malignancy in these patients. The first step involves the development of HIV-induced immunodeficiency that is manifested by an increased incidence of opportunistic infection. The exaggerated or prolonged clinical response to viral infection represents the second step, resulting in tumor development. Although our patient has no evidence of malignancy despite a careful search, one might speculate that the initial accelerated growth of her right auricular mass might have occurred secondary to immune modulation caused by HIV. The course of ALHE in this patient may continue to be modified by the presence of HIV.

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ANALYSIS OF PREVALENCE OF HUMAN PAPILLOMAVIRUS IN LARYNGEAL CARCINOMAS

STUDY OF 40 CASES USING POLYMERASE CHAIN REACTION AND CONSENSUS PRIMERS

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In this study we determined the frequency of association of human papillomavirus (HPV) and laryngeal carcinomas and investigated the possibility that HPV may be associated with larger or more aggressive tumors. Laryngeal squamous cell carcinomas from 40 patients who did not have preexisting papillomas by clinical history were retrieved from formalin-fixed, paraffin-embedded blocks and analyzed for HPV. Twenty-two cases were tumors of the true vocal folds, and 18 were supraglottic. Clinical follow-up was available for 25 patients. We used the polymerase chain reaction (PCR) with the "hot start" modification and consensus primers that can detect over 30 distinct HPV types. Three of the 40 patients (8%) had detectable HPV DNA. These 3 patients did not have unusual age demographics and were smokers. All but 1 of the 22 HPV-negative patients who were questioned were also smokers. We compared the outcomes for large (4 cm or greater) HPV-positive and -negative tumors. Six of the 40 tumors were 4 cm or greater and involved contiguous structures. Two of these 6 were HPV-positive, and these patients died of disease after 3 and 16 months, respectively. Of the 4 HPV-negative patients with tumors greater than 4 cm, 3 are disease-free at 41, 42, and 3 months, respectively, and 1 was lost to follow-up. The third HPV-positive patient had a tumor less than 1 cm, and is disease-free after 38 months. While the number of HPV-positive cases is too small for definitive conclusions, it is possible that for large tumors the presence of HPV DNA may portend a worse prognosis. However, in the population of patients with laryngeal carcinoma whom we have studied, we conclude that the L1 region of HPV DNA is rarely seen to be present in the tumors by "hot start" PCR, and hence HPV is probably not a common cancer promoter for laryngeal carcinoma.

KEY WORDS — consensus primer, "hot start" technique, human papillomavirus, larynx cancer, polymerase chain reaction.

INTRODUCTION

The association between human papillomavirus (HPV) infection and malignant and premalignant lesions of the uterine cervix, vulva, penis, and conjunctival[1] and periungual regions[2] has been well established. Infection with HPV has been associated with benign lesions of the upper aerodigestive tract, such as laryngeal papillomas,[3,4] and in the mucosa adjacent to laryngeal papillomas.[5] Malignant degeneration may occur in these benign laryngeal and tracheal papillomas, and HPV has been found in these neoplasms.[4,6-8]

Given the association between HPV and various mucosal lesions, HPV DNA has been sought in malignancies of the head and neck not associated with preexisting papillomas. Laryngeal verrucous carcinomas, like their counterpart in the lower genital tract, may harbor HPV.[9] Previous series using Southern blot and in situ hybridization techniques and type-specific probes found a low prevalence of HPV in laryngeal cancers, from 0% to 12.9%.[10-17] By the more sensitive polymerase chain reaction (PCR) technique, 20.6% to 54% of laryngeal cancers were found to harbor HPV.[16,18-20] The explanation for this large range may include false positives from nonspecific amplification or contamination or, conversely, insufficient numbers of HPV types in the probe cocktail–primer mixture. We determined the incidence of HPV infection in laryngeal cancers by using "hot start" PCR, which minimizes false positives from nonspecific DNA synthesis, with consensus primers that can detect over 30 distinct HPV types, in an attempt to maximize HPV detection.

MATERIALS AND METHODS

The cases examined were all from Mount Sinai Hospital, seen between the years 1988 and 1991. There is a trend of referral of laryngeal cancers to this institution for conservative surgery on small tumors (Table 1). One block of tumor was examined from each case, with two or three curls per block used. Paraffin blocks were cut by hand with sterile tech-

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REPRINTS — Gerard J. Nuovo, MD, Dept of Pathology, SUNY at Stony Brook, Stony Brook, NY 11794-8691.

TABLE 1. SUMMARY OF CASES STUDIED WITH CONSENSUS PRIMER AND RESULTS

	Tumor Size (cm)				
	<1	*1 to 1.9*	*2 to 2.9*	*3 to 3.9*	*>4*
Supraglottic	1	2	6	5	4 (2)
Glottic	10 (1)	8	1	2	1
Total	11	10	7	7	5

Numbers of cases positive for human papillomavirus are in parentheses.

nique and a disposable scalpel to avoid cross-contamination between samples. The tissues were deparaffinized with xylene, which was removed with 95% ethyl alcohol. The tissues were resuspended in sterile water and boiled at 100°C for 10 minutes. The DNA was solubilized by treatment with proteinase K (1 mg/μL) at 55°C for 3 hours. The proteinase K then was activated at 95°C for 10 minutes. The PCR was done with HPV consensus primers (Perkins Cetus). The consensus primers amplify a conserved L1 region of HPV types 1A, 2, 5, 6, 8, 11, 13, 16, 18, 26, 27, 30, 31, 33, 35, 39, 40, 41, 42, 43, 44, 45, 47, 48, 51, 52, 53, 54, 55, 57, 58, and 59.[21] The L1 region has been detected in the majority of cervical carcinomas. The PCR protocol has been previously published.[22] The following two modifications to the protocol were made.

1. The use of the "hot start" technique.[23,24] The DNA polymerase is withheld until the reaction temperature reaches 80°C. This additional step prevents nonspecific annealing of primers to human DNA ("mispriming") or to themselves (primer oligomerization), which may yield false-positive amplification and interfere with detection of viral DNA. This may be seen as either a false-positive reaction when labeled nucleotides are incorporated, or a false-negative reaction when Southern blot hybridization with a probe is performed.

2. Direct incorporation of digoxigenin-11-dUTP, which was visualized according to the manufacturer's recommendations (Boehringer Mannheimer, Indianapolis, Ind) as previously reported.[22] Negative controls used were normal lymph nodes from unrelated cases. Positive controls for the consensus primer were cervical tissues known to contain HPV and the cell line SiHa, which contains one integrated copy of HPV 16 per cell. After amplification, electrophoresis was performed and the DNA was transferred to nitrocellulose filters. The filters were probed under nonstringent conditions with ^{32}P-labeled probes for HPV 6, 11, 16, 18, 31, 35, and 51 as previously reported.[22] The PCR was repeated on positive cases to determine viral type. In order to determine that tissue decalcification did not degrade tissue DNA, positive tissue controls for the BCL-2 gene were run in five decalcified and five nondecalcified samples.

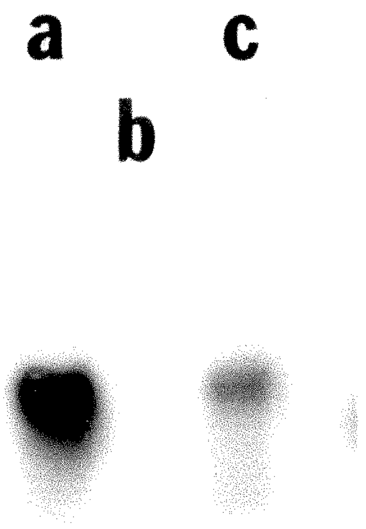

Fig 1. Detection of human papillomavirus (HPV) DNA with consensus primers by polymerase chain reaction. Amplified HPV DNA was detected with ^{32}P-labeled probes in squamous cell carcinoma of larynx (lane c). Lane a — amplified HPV 16 DNA from SiHa cells that served as positive control, lane b — negative genital tract lesion.

RESULTS

Forty patients were studied (32 men and 8 women), ages 34 to 77 (mean age 57). Table 1 compiles information about the tumors according to site, tumor size, and HPV results. Detection of amplified HPV DNA was seen in 3 of the 40 cases studied (8%; Fig 1). In each of the decalcified tissues, amplified endogenous DNA was detectable. Of the 3 HPV-positive cases, 1 was found to contain HPV 16, and the other 2 contained a type related to but distant from the HPVs used in the detection probe cocktail.

All but one patient questioned (who was HPV-negative) had a history of cigarette smoking from 5 to more than 100 pack years. One patient had a history of irradiation treatment in the 1930s for a skin condition, while some of the patients had occupational histories involving exposures to carcinogens such as asbestos. Two patients were directly involved in construction labor including asbestos exposure. One patient was a postal worker who was indirectly exposed to welding and asbestos at the work site. One patient was a metal worker who also developed squamous carcinoma of the nasal septum. One patient was a tile setter with exposures to adhesives; one worked in a nuclear power plant.

TABLE 2. COMPARISON OF INCIDENCE OF HPV IN LARYNGEAL SQUAMOUS CARCINOMAS WITHOUT PAPILLOMAS

Authors	*Year*	*Technique*	*HPV Types*	*No. of Cases*	*% Positive*
Kahn et al[10]	1986	SB	30	42	2.3
Scheurlen et al[11]	1986	SB	16	36	2.7
Stremlau et al[12]	1987	SB	1, 2, 4, 8-11, 13, 16, 18	30	10
Syrjänen et al[13]	1987	ISH	6, 11, 16, 30	116	12.9
Löning et al[14]	1987	DB	6, 11, 16, 18	5	40
Brandsma and Abramson[15]	1989	SB	6, 11, 16, 18, 31	60	5
Kiyabu et al[18]	1989	PCR	16, 18	10	40
Ishibashi et al[17]	1990	SB	1, 5, 6, 11, 16-18, 20	3	0
Hoshikawa et al[19]	1990	PCR	6*B*, 16	34	20.6
Pérez-Ayala et al[20]	1990	PCR	11, 16	48	54
Somers et al[16]	1990	SB	2, 6, 11, 16, 18, 30 31, 33, 35	25	4
This study		PCR*	1*A*, 2, 5, 6, 8, 11, 13, 16, 18, 26, 27, 30, 31, 33, 35, 39-45, 47, 48, 51-55, 57-59	40	8

HPV — human papillomavirus, SB — Southern blot, ISH — in situ hybridization, DB — dot blot hybridization, PCR — polymerase chain reaction.

*"Hot start" modification.

Follow-up data were obtained on 25 of the 40 patients. Of the 3 HPV-positive cases, 2 patients (tumors over 4 cm) are dead of disease at 3 and 16 months, and 1 patient (tumor less than 1 cm) is disease-free at 38 months. Of the HPV-negative cases, all but 1 patient are alive. Seventeen patients (all tumor sizes) are disease-free at a mean follow-up of 36 months. Two patients (1 with a tumor less than 1 cm and 1 greater than 3 cm) are alive with disease at 42 and 35 months, respectively. One patient (tumor greater than 1 cm) is disease-free after salvage surgery at 34 months, and 1 patient (tumor over 2 cm) is dead of disease after 24 months. One patient had surgery only recently.

DISCUSSION

Tumors and premalignant conditions of the lower genital tract have been extensively studied for over a decade, and HPV has been established as a significant cofactor in carcinogenesis. For upper aerodigestive tract carcinomas, there is controversy over the incidence of HPV infection and its possible significance as an oncogenic cofactor. Human papillomavirus has been detected anecdotally in various squamous carcinomas of the tongue,[15,16,25] oral cavity,[14,26,27] tonsil, and maxillary sinus.[17] Southern blot investigation by Brandsma and Abramson[15] revealed 18%, 29%, and 13% rates of HPV detection in tongue, tonsil, and pharynx carcinomas, respectively, as compared to 5% for larynx carcinoma. Infections with HPV were not detected in clinically and histologically normal tissues of the tongue, tonsil, and pharynx in the study of Brandsma and Abramson, but a 4% prevalence of latent HPV infection was found in the benign larynx by Southern blot hybridization.[15] Thus, there is an emerging trend of site preference for HPV and head and neck cancers. Site preference has been documented in the female genital tract cancers, in which HPV is invariably associated with cervical cases, occasionally with vulvar cases,[2] and rarely, if ever, with endometrial cancers.[28] Very little is known about the actual mode of HPV transmission in the upper aerodigestive tract, or the period of latency.

This study was designed to maximize detection of a large number of HPV types in one type of cancer, in an attempt to establish infection prevalence. Our data were obtained by employing the hot start PCR technique with consensus primers. The hot start method increases the sensitivity of amplification by inhibiting nonspecific primer annealing.[24] Unwanted DNA synthesis from mispriming and primer oligomerization interferes with specific amplification, resulting in false-negative results when Southern blot hybridization analysis is performed. The consensus primer pair can detect a conserved region present in over 30 HPV types. With this enhanced detection sensitivity, we have demonstrated a low prevalence (8%) of HPV DNA in laryngeal carcinomas. The prevalence of HPV infection in laryngeal cancers has ranged from 3% to 40%[10-12,14-16] by the Southern blot and dot blot hybridization techniques to 20% to 54%[18-20] by the PCR technique (Table 2[10-20]). Our study tested for more HPV types, and theoretically could have resulted in an even higher infection rate; however, we found our infection rate to be closer to those found by most Southern blot studies.

A number of factors may account for the observed difference in HPV detection rates. In the three previous PCR studies the detection rate of HPV 6, 11, or 16 ranged from 20% to 54%.[18-20] The PCR is an exquisitively sensitive tool, susceptible to false positives from a variety of sources such as contaminants.

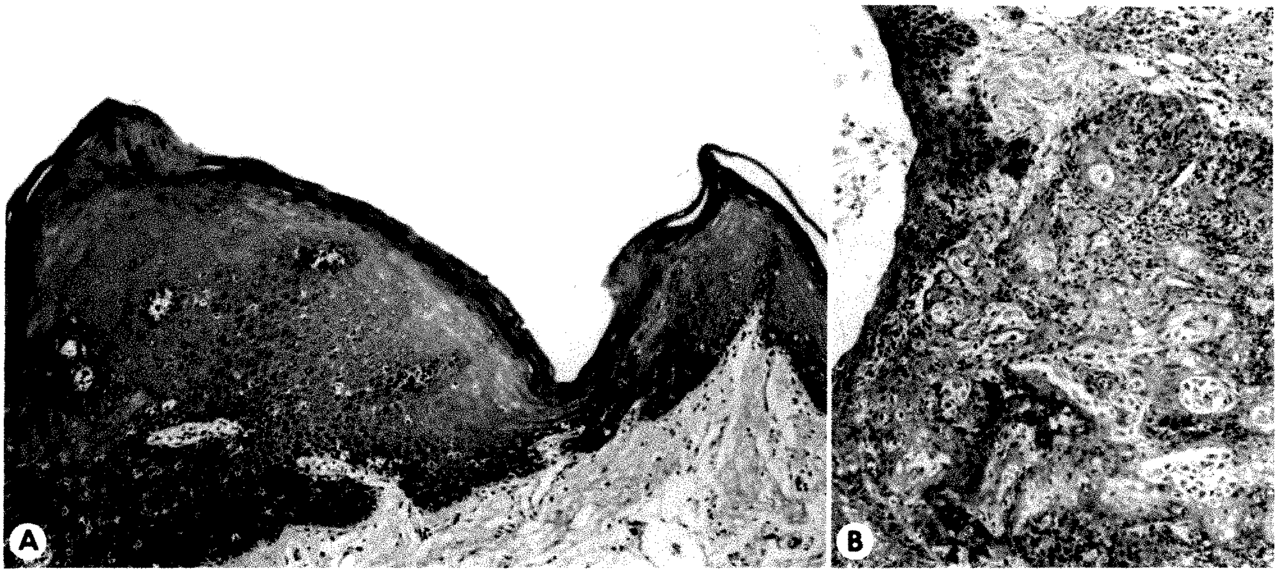

Fig 2. A) Laryngeal mucosa adjacent to B) carcinoma. Parakeratosis and "spirelike" formation are vaguely reminiscent of verruca vulgaris. This case contains no detectable human papillomavirus DNA.

As the study by Kiyabu et al[18] contained many positive samples from other sites, the 40% detection rate might be influenced by false positives. Nonspecific amplification of human DNA as a result of mispriming is another significant problem. The product of a misprimed event can be exponentially amplified. Furthermore, if the Southern blot technique is then performed and an HPV probe is hybridized under nonstringent conditions, a false-positive signal might be detected because of homology between human DNA and HPV.[23,24] This phenomenon does not occur with the hot start modification. This modification in technique was not performed in the studies of Pérez-Ayala et al[20] or Hoshikawa et al.[19]

It is also possible that the lower rate of HPV DNA detection in our study may reflect DNA degradation after tissue decalcification. The studies of Hoshikawa et al[19] and Pérez-Ayala et al[20] were performed on nondecalcified tissues. However, a positive tissue control using decalcified tissue from this study group and the ubiquitous BCL-2 gene showed all cases to be positive, indicating that the decalcification solution used (10% formalin, 10% formic acid) probably did not result in DNA degradation. We have noted that RNA and DNA remain amplifiable after decalcification in a variety of bony tissues and cell lines (G.J.N., unpublished observation).

Tumor size and grade may in some way correlate with the presence or absence of HPV; however, the numbers studied are still small, and contradictory trends have been seen. The incidence observed by Hoshikawa et al, of 20.6% HPV positivity, was obtained in large tumors (clinically staged as T3 and T4 exclusively),[19] while more than half of our cases (20 of 39) were pathologically staged from microscopic to 2 cm. However, 2 of our 3 positive cases were from the six tumors studied greater than 4 cm. We could not identify any relevant epidemiologic differences between the HPV-positive and HPV-negative patients, although given the small sample size, this would have been expected. Pérez-Ayala et al[20] do not mention tumor stage in their study, but they do note that their positive cases tended to be poorly differentiated carcinomas. This trend for less-keratinizing carcinomas to contain HPV has been previously observed for vulvar carcinomas.[28] However, this trend could not be supported by the study of Hoshikawa et al or our work. Only 1 case of 10 (the 7 positive cases of Hoshikawa et al[19] and our 3 positive cases) was poorly differentiated. On the other hand, Löning et al[14] noted the trend of a group of mixed-site upper airway carcinomas with HPV infection to be better differentiated.

A further consideration is that geographic population might influence the prevalence of HPV in the upper aerodigestive tract. The study group of Pérez-Ayala et al[20] was from Granada, Spain, while the group of Hoshikawa et al[19] was from Tokyo, Japan.

Our study suggests that HPV is not a common cofactor for carcinoma of the larynx. Figure 2 illustrates a carcinoma that might have led one to predict the presence of HPV; it has surface spirelike mounds of parakeratosis and papillaelike structures. But by this most sensitive and broadest detection method, it is HPV-negative. This supports that the same histologic findings strongly suggestive for the presence of HPV in the genital tract, eg, koilocytosis, etc, when seen in the larynx may lack specificity for HPV.

Further, those larger (over 4 cm) tumors that do contain HPV may be associated with a worse outcome; however, the numbers studied are too small for definite conclusions. Explanations for the observations await further study, which should include analysis of cell lines derived from head and neck cancers for HPV, given the well-documented ability of HPV to immortalize cell lines.

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EFFECTS OF NASAL ALLERGEN CHALLENGE ON DYNAMIC VISCOELASTICITY OF NASAL MUCUS

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The effects of nasal provocation on the rheologic properties of nasal mucus were investigated in patients with allergic rhinitis provoked by house dust. The elastic modulus (G′) and the dynamic viscosity (η′) of nasal mucus were determined by an oscillating sphere magnetic rheometer. Before and after the allergen challenge, G′ increased, whereas η′ decreased with increasing oscillatory frequency; these findings indicate that the nasal mucus under these conditions is a non-newtonian fluid and has the cross-linked gel-like nature typical of mucus. Both G′ and η′ values after nasal provocation were significantly lower than before. The values of G′ and η′ after allergen challenge were in the optimal viscoelasticity range for mucociliary transport.

KEY WORDS — allergic rhinitis, elasticity, nasal mucus, nasal provocation, viscosity.

INTRODUCTION

Nasal fluid is a mixture derived from goblet cells, submucosal glands, anterior serous glands, lacrimal glands, condensed water from expirated air, and a variable degree of transudation from blood vessels and tissue.[1] Excessive watery nasal discharge is a characteristic feature of allergic rhinitis, and it contains mainly mucous glycoproteins, but also contains serum glycoproteins in a small amount.[2] Although mucous glycoproteins largely contribute to the viscoelasticity of nasal fluid in allergic rhinitis, little is known about the rheologic properties. The aim of this study is to investigate these properties before and after nasal provocation with allergen in patients with allergic rhinitis.

MATERIALS AND METHODS

Subjects and Experiment. Thirteen patients (8 male and 5 female, age 12 to 42 years, mean 22.4 years) had allergic rhinitis diagnosed on the basis of clinical history, rhinoscopic findings, nasal eosinophilia, and a positive radioallergosorbent test to house dust. As a control, each patient received a small paper disc without allergen on the nasal mucosa of the inferior turbinate. If the patient did not complain of any symptoms, nasal provocation was performed with a provocation disc with house dust allergen (250 µg dry weight; Torii Yakuhin Co Ltd, Tokyo, Japan). All of the patients showed allergic symptoms such as sneezing, nasal obstruction, and rhinorrhea within 15 minutes after the nasal provocation with allergen.

Nasal mucus was collected by aspiration from the nasal cavity both before and after nasal provocation. Care was taken to avoid stimulating the nasal mucosal surface during the prechallenge aspiration. The postchallenge collection of nasal mucus was performed 10 minutes after the allergen challenge. All investigations were carried out in the morning. The collected mucus was stored in a small tube to prevent its evaporation, and frozen at −80°C.

Measurement of Dynamic Viscoelasticity. The viscoelasticity of the nasal mucus was determined by an oscillating sphere magnetic rheometer.[3] Approximately 4 µL of the test sample together with a small iron sphere with a radius of 100 µm was put into the sample cell, which was placed in the space between the upper and lower magnetic poles. The iron sphere was oscillated in a vertical direction by application of sinusoidally varying magnetic field gradients. The motion of the iron sphere was followed through a light microscope and transduced to an electrical signal with an optoelectrical tracker.

Dynamic viscoelasticity was calculated according to the following formulas using the given values of the amplitude of the displacement of the iron sphere (Xo), and the phase lag of the sphere (δ, rad) with respect to the oscillatory driving force (Fo, dyne):

$$(1)\quad \text{Elastic modulus } G' = \frac{Fo}{6\pi rXo}\cos\delta + \frac{2}{9}\rho Sr^2\omega^2$$

$$(2)\quad \text{Dynamic viscosity } \eta' = \frac{Fo}{6\pi rXo\omega}\sin\delta$$

where r is the radius (cm) of the iron sphere, ρS is the

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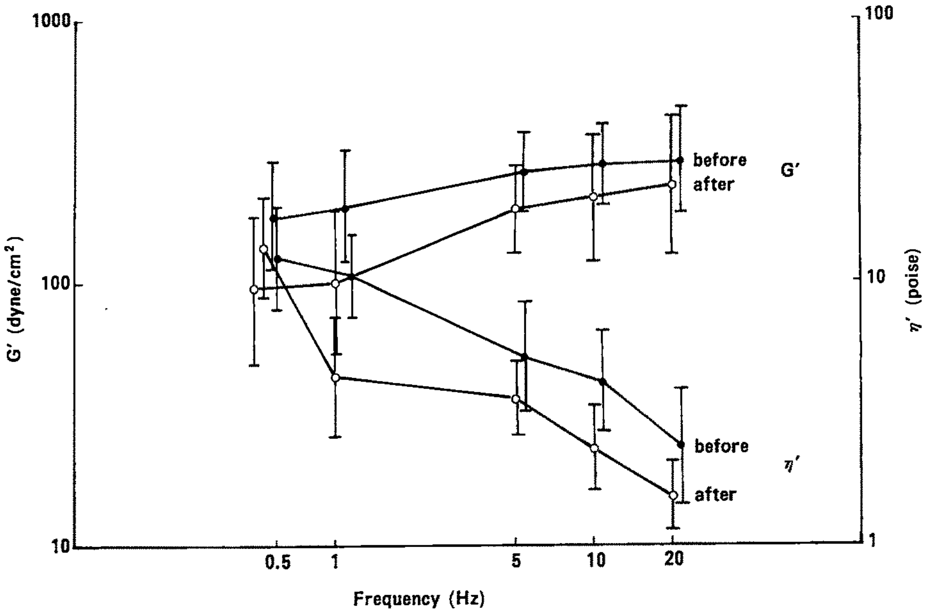

Fig 1. Elastic modulus (G') and dynamic viscosity (η') of nasal mucus both before (closed circles) and after (open circles) allergen challenge in patients with house dust allergy.

density of the sphere (g/cm^3), and ω is the angular frequency (rad/s). G' is indicative of elastic behavior, while η' is a measure of the viscous behavior of the sample. Both G' and η' were determined at 25°C at frequencies of 0.5, 1, 5, 10, and 20 Hz.

Statistical Analysis. Since the variations in G' and η' were logarithmically distributed, the data were subjected to common logarithmic transformation. The significance of the change in rheologic properties before and after the provocation was evaluated with the paired *t* test. A p value less than .05 was considered significant. The values are stated within the text as mean ± 1 SD.

RESULTS

Spectrum of Dynamic Viscoelasticity. Figure 1 shows the elastic modulus (G') and dynamic viscosity (η') of nasal mucus from patients both before and after provocation with allergen. In the frequency range from 0.5 to 20 Hz, G' increased along with the increase of the frequency, and η' decreased.

Effect of Provocation on Elastic Modulus. The G'

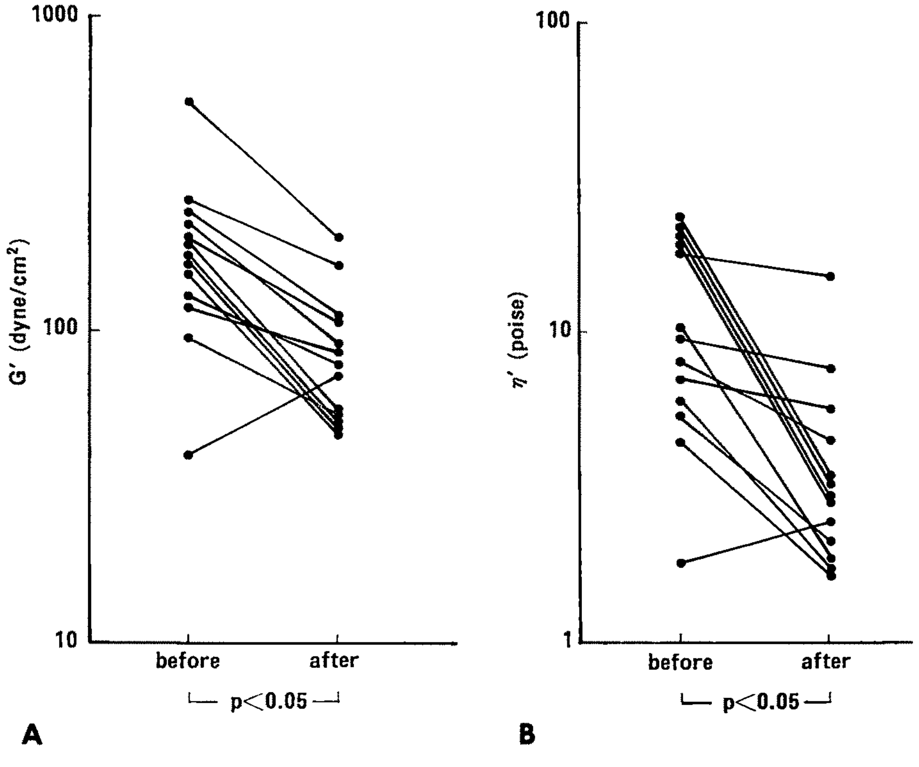

Fig 2. A) Elastic modulus (G') and B) dynamic viscosity (η') values of nasal mucus at 1 Hz before and after provocation. Both values after provocation were significantly lower than those obtained before allergen challenge ($p < .05$).

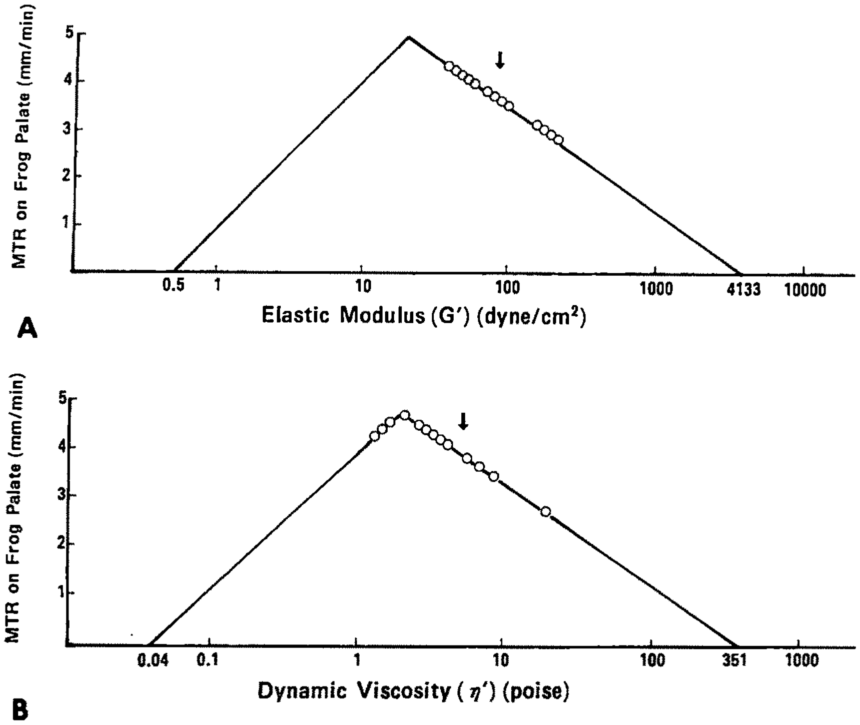

Fig 3. Relationship between mucociliary transport rate and viscoelasticity. Graph shows relationships between A) elastic modulus (G') and B) dynamic viscosity (η') of human middle ear effusions (mucus) at frequency of 1 Hz (25°C) and mucociliary transport rate (MTR) of effusion on mucus-depleted frog palate.[15] G' and η' values of nasal mucus obtained after allergen challenges were plotted on line. Arrow — mean values of G' and η'.

values of the nasal mucus after provocation were significantly lower than those obtained before the provocation test ($p < .05$; Fig 2A). Before provocation, the G' values at 1 Hz ranged from 40 to 532 dyne/cm^2 (geometric mean 193 ± 117 dyne/cm^2). After provocation, they ranged from 51 to 198 dyne/cm^2 (geometric mean 89 ± 46 dyne/cm^2).

Effect of Provocation of Dynamic Viscosity. The η' values of the nasal mucus after the provocation test were significantly lower than those obtained before provocation ($p < .05$; Fig 2B). Before provocation, the η' values at 1 Hz ranged from 4.5 to 21 poise (geometric mean 12 ± 7.4 poise). After provocation, they ranged from 1.7 to 15 poise (geometric mean 4.1 ± 3.7 poise).

DISCUSSION

In the present study, the effects of allergen challenge on rheologic properties in the early phase response were examined. The nasal mucus samples were collected 10 minutes after the allergen challenge, because the concentrations of inflammatory mediators rise for 20 minutes,[4] and the maximum nasal mucus production exists about 5 minutes after the allergen challenge.[5] The nasal mucus before and after allergen challenge showed an increase in elasticity (G') and a decrease in viscosity (η') with increasing frequency, as shown in Fig 1. The curves of G' and η' versus frequency obtained in the present study are similar to those observed in studies of nasal mucus from chronic sinusitis[3] and tracheobronchial mucus.[6] That the shape of the curves is characteristic of all fluids of long-chain molecules and of the nonnewtonian fluids indicates that nasal mucus both before and after allergen challenge has the cross-linked gel-like nature typical of mucus. Our findings are consistent with those of a biochemical analysis of nasal fluid by Brofeldt et al.[2] They reported that nasal provocation with allergen produces nasal secretion mainly containing glycoproteins of a mucous type, such as fucose, that probably form a stronger gel.

In this study, the rheologic properties of nasal mucus samples were determined after storage at −80°C, because Charman and Reid[7] reported that freezing and storage at −70°C prevents the degradation of the rheologic properties of sputum. Before the allergen challenge, the mean value at 1 Hz of G' was 193 dyne/cm^2 and the mean value of η' was 12 poise. In our previous study of nasal mucus from 75 adult patients with chronic sinusitis, we found that the mean value at 1 Hz of G' was 2,536 dyne/cm^2 (253.6 Pa) and that of η' was 255 poise (25.5 Pa/s).[8] These results show that both the elasticity and the viscosity of nasal mucus in allergic rhinitis are much lower than in chronic sinusitis.

After allergen challenge, the elasticity and the viscosity of nasal mucus were found to be significantly lower than before the challenge. It is not known which factors influence the decrease, but the increase in secretory rate from the nasal glands may partly contribute, because Jeanneret-Grosjean et al[9] have found an inverse correlation between viscoelasticity and the amount of tracheobronchial mucus in normal humans. The changes in active ion transport of the nasal epithelium after allergen challenge also decrease the viscoelasticity by leading to an increase in fluid transport toward the lumen.[10]

It seems likely that the altered composition of nasal mucus after allergen challenge may influence nasal mucociliary clearance. In patients with nasal allergy, conflicting results have been reported as regards mucociliary clearance. Kaya et al,[11] using radiolabeled resin particles, reported an obvious decrease in nasal mucus flow rate in allergic patients. Guercio et al[12] observed an impairment of nasal mucociliary transport after intranasal instillation of ragweed extract in patients with ragweed rhinitis. On the other hand, Ukai et al,[13] using the saccharin method, showed no demonstrable reduction of nasal mucociliary clearance in patients with perennial rhinitis. Wihl and Mygind[14] failed to demonstrate a prolongation of the saccharin time after local application of timothy pollen grains. It is well known that the rheologic properties, especially elasticity and viscosity, of mucus are important determinants of the mucociliary system. In our previous study, the maximum mucociliary transport rate (MTR) of mucus on mucus-depleted frog palate (beating cilia) was achieved when the value of G' was 20 dyne/cm^2 and that of η' was 2 poise at a frequency of 1 Hz (25°C).[15] There was a significantly positive correlation between the MTR and G' or η' at values lower than the optimal viscoelasticity. A significantly negative correlation was also observed between the MTR and G' or η' at values higher than optimal (Fig 3[15]). The G' and η' values of nasal mucus at 1 Hz obtained after allergen challenge in our present study are shown in Fig 3 on the line indicating the relationship between MTR and G' or η'. It can be seen from this Figure that both G' and η' after allergen challenge are in the optimal ranges for mucociliary transport. These results suggest that the rheologic properties of nasal mucus itself could not impair nasal mucociliary clearance in the early phase of the allergic response.

Mygind[5] reported that watery secretion starts about the time of the last sneeze after allergen challenge, continues for some minutes, and then changes, macroscopically, to a viscid seromucus. Thus, the rheologic measurement of nasal mucus during the late phase of allergic response must be studied in further experiments.

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IMAGING CASE STUDY OF THE MONTH

LYMPHOMA OF THE SPHENOID SINUS PRESENTING AS AN EXPANSILE MASS

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CASE REPORT

A 39-year-old man presented to the emergency room with a sensation of pressure and congestion in the left side of the nose and above the left eye. He also had an upper respiratory tract infection. The findings on physical examination were unremarkable.

On a follow-up visit 2 weeks later, there was again nasal congestion on the left. In addition, the patient complained of pain and paresthesia of the left cheek. There was epiphora of the left eye. On physical examination, there was diffuse facial tenderness and temporomandibular joint tenderness on the left.

On review of the paranasal sinus films, there was some increased density in the sphenoid sinus with poor definition of the sella turcica. The remaining sinuses were normal. A computed tomography (CT) scan of the paranasal sinuses in the axial and coronal (Fig 1) planes following introduction of contrast material revealed a slightly enhancing soft tissue mass within the sphenoid sinus with extension to the sella turcica. There was no extension into the suprasellar cistern.

For further evaluation of the tumor, a magnetic resonance imaging (MRI) study was performed. A sagittal section was carried out with a T1-weighted pulse sequence (Fig 2A). This was supplemented with axial pregadolinium (Fig 2B) and postgadolinium (Fig 2C) T1-weighted images and axial T2-weighted images (Fig 2D). The sphenoid mass revealed a low signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. There was slight to moderate enhancement following the introduction of gadolinium. There was erosion into the clivus and sella and extension through the floor of the sphenoid sinus and into the left nasal cavity. The mass penetrated through the left lateral wall of the sphenoid sinus with abutment on the left cavernous sinus.

The diagnosis of malignant lymphoma (diffuse large T-cell type) was established with a transsphenoidal biopsy. Simultaneously, a bone marrow right iliac crest biopsy was performed; it revealed no malignant cells. Subsequently, the patient underwent a 31-day course of radiotherapy followed by chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and methotrexate.

DISCUSSION

Lymphoma of the paranasal sinuses is relatively rare, compared with the occurrence of carcinoma of the paranasal sinuses.[1-3] According to a report by the Kiel Lymph Node Registry, which tabulated all such cases between 1972 and 1987 (a total of 59 cases), these lymphomas constituted about 0.17% of all malignant lymphomas and 0.44% of all extranodal malignant lymphomas.[4] The median age in that

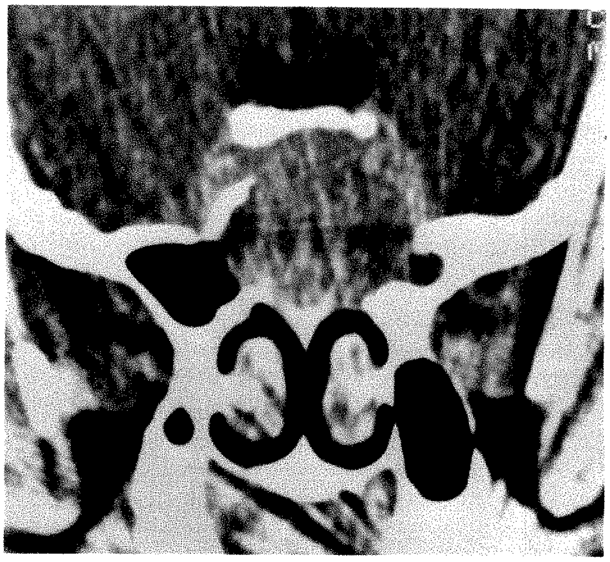

Fig 1. Coronal computed tomographic scan following introduction of contrast medium reveals homogeneous, slightly enhancing mass in sphenoid sinus with extension into sella turcica. There is partial erosion of sphenoid sinus and sella.

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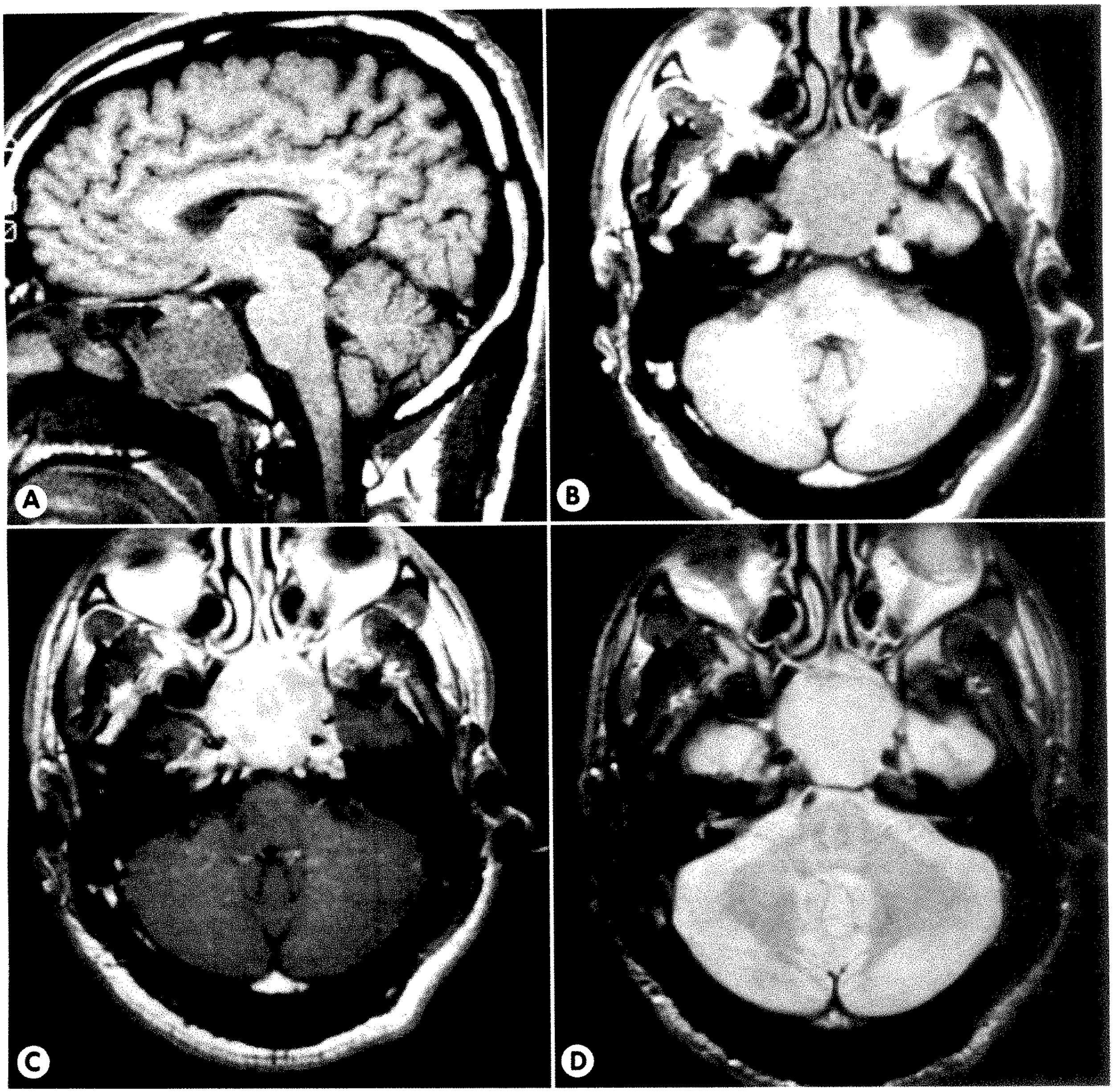

Fig 2. Magnetic resonance imaging. A) Sagittal T1-weighted image shows expansile mass in sphenoid sinus with extension into sella turcica, clivus, and upper anterior portion of nasopharynx. B,C) Five-millimeter axial T1-weighted images B) before and C) after administration of gadolinium show moderate enhancement of tumor. D) Axial T2-weighted image shows moderately increased signal intensity of this expansile lesion, which bulges into left and right cavernous sinus and into posterior portion of ethmoid sinus.

study was about 64.5 years, and there was a female predominance. In that series, the predominant cell type was B-cell lymphoma, while T-cell lymphomas were in the minority (5 of 59).

In a separate report of 20 malignant lymphomas of the paranasal sinuses and nasal cavity, Weber et al (unpublished observations, 1987) found 5 low-grade lymphomas and 15 high-grade lymphomas. The histologic breakdown of these 20 cases (based on the Kiel classification) is given in the Table. Extranodal Hodgkin's lymphoma is rare in the head and neck region.[1]

The clinical signs and symptoms of malignant lymphoma of the paranasal sinuses include a mass in the nasal cavity, facial pain, paresthesia, recurrent sinusitis, nasal discharge, and, if orbital invasion has occurred, eyelid swelling and proptosis (Weber et al, unpublished observations, 1987). In this analysis of 20 cases of lymphoma, multiple sinuses were involved in 7 cases, which is a reflection of the advanced stage of these tumors by the time the diagnosis was established; 6 cases involved the maxillary antrum, and 3 cases the ethmoid sinuses.

The radiographic evaluation constitutes an important part of the diagnosis of these lesions. Conventional films are of limited value, since they do not

PATHOLOGIC EVALUATION OF 20 CASES OF MALIGNANT LYMPHOMA OF PARANASAL SINUSES AND NASAL CAVITY

	No. of Cases	
Low grade		5
Lymphoplasmacytoid	2	
Centroblastic or centrocytic	3	
High grade		15
Centroblastic	8	
Immunoblastic	1	
Burkitt's lymphoma	2	
Large cell anaplastic	4*	

Data from Weber et al (unpublished observations, 1987). Kiel classification of non-Hodgkin's lymphoma is used.

*Including T-cell lymphomas.

depict, in detail, bone destruction (which represents one of the hallmarks of the diagnosis of a malignant tumor). Likewise, extension of these tumors is difficult to accurately assess with conventional sinus films. The studies of choice for malignant lesions of the paranasal sinuses, including malignant lymphomas, are CT and MRI.

The CT sections depict the soft tissue component clearly, and with bone window settings, bony expansion and bone destruction are demonstrated.[2] By using both soft tissue and bone window settings, the tumor can be demonstrated within the sinus cavity, and extension into the adjacent structures can be mapped out in detail. Extension of malignant lymphomas into the pterygopalatine fossa, infratemporal fossa, orbits, and intracranial cavity may occur.[5] Axial and coronal sections are mandatory for depicting the extension into the various anatomic structures. Malignant lymphoma of the paranasal sinuses may manifest as an expansile lesion and thereby mimic a benign lesion. However, in most cases, the tumor is advanced and permeative bone destruction is present.

The CT and MRI findings are not specific and do not allow a histologic diagnosis of lymphoma. Because of the higher contrast, MRI has the added advantage of defining the interface between the lesion and adjacent structures in greater detail.[6-9] Moreover, as in other malignant sinus tumors, MRI is capable of differentiating retained secretions or edematous inflamed mucosa from the tumor proper.[8,10] This is best accomplished with T2-weighted images, in which the tumor is usually of intermediate signal intensity, while secretions and edematous mucosa are of high signal intensity.[10]

Following the introduction of gadolinium, there was slight to moderate enhancement, as is encountered in most other malignant paranasal sinus tumors.[6,7] Extension of malignant tumors, including lymphoma, into the intracranial cavity is best defined with MRI after gadolinium injection.[5] The interface between the tumor, extradural space, and/or brain is usually of sufficient contrast to allow accurate assessment. In addition, MRI has the advantage of providing sections in multiple planes. The sagittal plane is especially useful in the assessment of midline and parasagittal lesions, as was demonstrated in our case, in which the sphenoid sinus tumor was well depicted on the sagittal plane (Fig 2A).

In the differential diagnosis, a variety of other lesions should be considered. Carcinoma is rare in the sphenoid sinus and causes permeative bone destruction with irregular and less well-defined margins. Solitary plasmacytoma is infrequent in this location, but displays identical features on CT and MRI. Metastasis may occur in this location and mimic an expansile lesion.[11]

A chondrosarcoma may arise in the sphenoid sinus and display expansile features without significant bone destruction. Some chondrosarcomas contain speckled, mottled, or curvilinear calcifications that provide a clue in the diagnostic evaluation. Some chondrosarcomas, however, reveal no calcification and simulate other types of tumors. To demonstrate small areas of calcification, CT is the method of choice. With MRI, only large areas of calcification are displayed.

The mucocele represents the most common lesion in the sphenoid sinus. A mucocele may occupy a compartment of the sphenoid sinus or involve the entire sinus cavity. Frequently, mucoceles expand slowly and cause remodeling of bone. There may be areas of dehiscence in the bony outline. Sharp definition with a thin bony rim suggests mucocele in the majority of cases. Moreover, MRI classically shows a marked increase in signal intensity on T2-weighted images. The T1 pulse sequence demonstrates variable signal intensities, depending on the type of fluid within the mucocele. Highly proteinaceous fluid demonstrates a high signal intensity, while inspissated, viscous material usually displays a low signal intensity. Following the introduction of gadolinium, the fluid content of a mucocele will not enhance. However, there may be slight enhancement of the wall, especially when there is superimposed inflammation.

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SIXTH INTERNATIONAL CONGRESS ON INTERVENTIONAL ULTRASOUND

The Sixth International Congress on Interventional Ultrasound will be held September 7-10, 1993, in Copenhagen, Denmark. For information, contact Christian Nolsøe, Congress Secretary, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

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INTERNATIONAL HEARING AID CONFERENCE
GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

An International Hearing Aid Conference will be held June 25-27, 1993, at The University of Iowa, Iowa City. For information on registration and accommodations, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

Ann Otol Rhinol Laryngol 102:1993

PATHOLOGY CONSULTATION

PERIPHERAL EPITHELIAL ODONTOGENIC TUMORS

JOHN G. BATSAKIS, MD
M. JOHN HICKS, MD, PHD　　CATHERINE M. FLAITZ, DDS, MS
HOUSTON, TEXAS

Peripheral epithelial odontogenic tumors are the extraosseous equivalents of the much more often encountered central gnathic odontogenic tumors. The peripheral tumors arise in the mandibular or maxillary gingiva from the surface mucosa or dental lamina rests in the submucosa. Ameloblastoma is the most common histologic type. It, like all other peripheral epithelial odontogenic tumors, follows a benign, nonaggressive clinical course.

A peripheral odontogenic tumor is one that manifests the histologic characteristics of its central or intraosseous counterpart, but which arises in the tooth-bearing soft tissues of the mandible and maxilla.[1,2] It is not associated with a demonstrable intraosseous tumor. On the basis of reports in the literature, peripheral odontogenic tumors are considered as rare lesions.[1,2] That frequency appears to be understated.

A considerable variety of odontogenic tumors take origin in the gingival soft tissues.[1] These include ameloblastoma, adenomatoid odontogenic tumor, calcifying epithelial odontogenic tumor, squamous odontogenic tumor, odontogenic fibroma (gingival epithelial hamartoma, ameloblastic fibrodentinoma), granular cell ameloblastic fibroma, and calcifying odontogenic cyst. The peripheral ameloblastoma is the most frequently encountered. It accounted for 26 of the 48 (54%) peripheral epithelial odontogenic tumors collected by Buchner and Sciubba[1] in their review of the English-language literature. Nauta et al[3] have subsequently confirmed this preponderance (see Table[3]). Approximately 5% of all ameloblastomas are claimed to be peripheral in origin.[2]

CLINICAL ASPECTS OF PERIPHERAL AMELOBLASTOMAS

Characteristics	*Findings*	
No. of cases	53	
Age at diagnosis (y)	16-92	Mean 50.2
Gender of patients		
Male	32	60%
Female	19	36%
Not stated	2	
Race of patients		
White	31	58%
Black	4	8%
Oriental	8	15%
Not stated	10	19%
Oral site (gingiva)		
Mandible	35	66%
Maxilla	18	34%
Follow-up period	6 mo to 8 y	Mean 33 mo
Recurrences (gingiva)	8	15%
Mandible	4	
Maxilla	4	
Recurrences after second excision	0	

Modified from Nauta et al.[3]

PERIPHERAL AMELOBLASTOMA

These lesions have the following clinical characteristics: male predisposition; wide age range at time of discovery (16 to 92 years; mean of 50.2 years and highest incidence in the fifth and sixth decades); apparent predilection for whites; mandibular prefer-

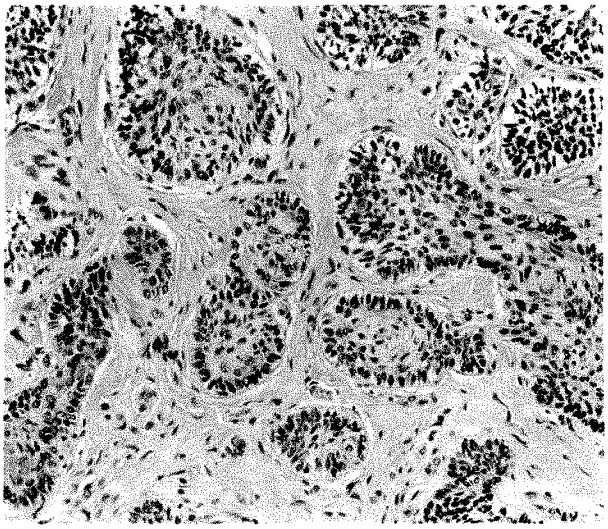

Fig 1. Peripheral ameloblastoma of mandibular gingiva (H & E, original x120). This lesion had no connection with overlying mucosa.

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.
REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

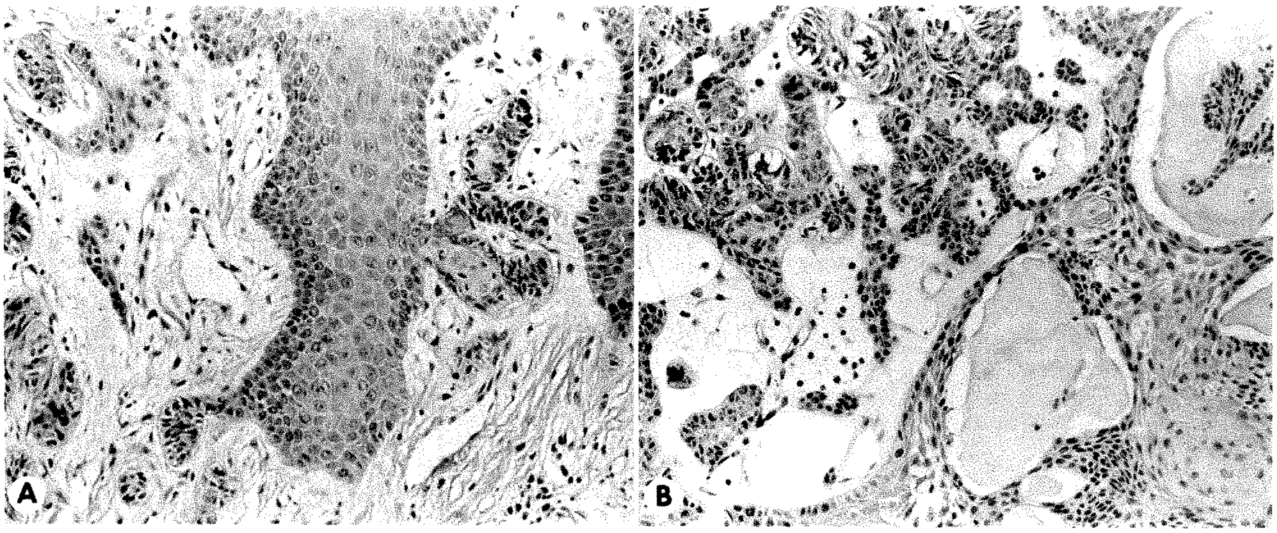

Fig 2. Peripheral ameloblastoma of surface origin and multifocal origin. A) Small ameloblastoma buds protrude from squamous mucosa (H & E, original x160). B) Separate focus of ameloblastoma showing acanthomatous areas in lower right (H & E, original x120).

ence (66% versus 34% in maxilla); a canine-premolar mandibular gingival location as opposed to a molar-retromolar maxillary site; 0.3 to 4.5 cm size at time of surgical removal; and no radiographic evidence of bone involvement except for occasional instances of superficial erosion or saucerization.[1-4]

Any histologic type of ameloblastoma can be found in the peripheral lesions, although an acanthomatous pattern is most often seen.[1]

In keeping with a proposed dual histogenesis, peripheral ameloblastomas without a continuity between the tumor and the gingival surface mucosa (Fig 1) are considered to arise from remnants of the dental lamina.[1,2,4] The majority, however, have continuity with the mucosa and can show multiple connection foci[1] (Fig 2).

The peripheral ameloblastoma is not an aggressive lesion. Invasion of bone is not a feature, and "cure" is usually achieved by conservative excision with adequate margins.[1-4] A potential for recurrence exists, perhaps because of multifocality. Nauta et al[3] record an 8% recurrence rate. Reexcision successfully controls the disease.

The controversy over whether the peripheral ameloblastoma and basal cell carcinoma of the oral mucosa are the same or two different lesions has been settled in favor of the former proposal.[1,4] Still unsettled, however, is whether extragingival peripheral ameloblastomas exist.[1] These lesions have been reported in the buccal mucosa and floor of the mouth, and their histogenesis has been attributed to the pluripotentiality of the oral epithelium. A malignant peripheral ameloblastoma is a theoretic possibility, but there are no well-documented cases.

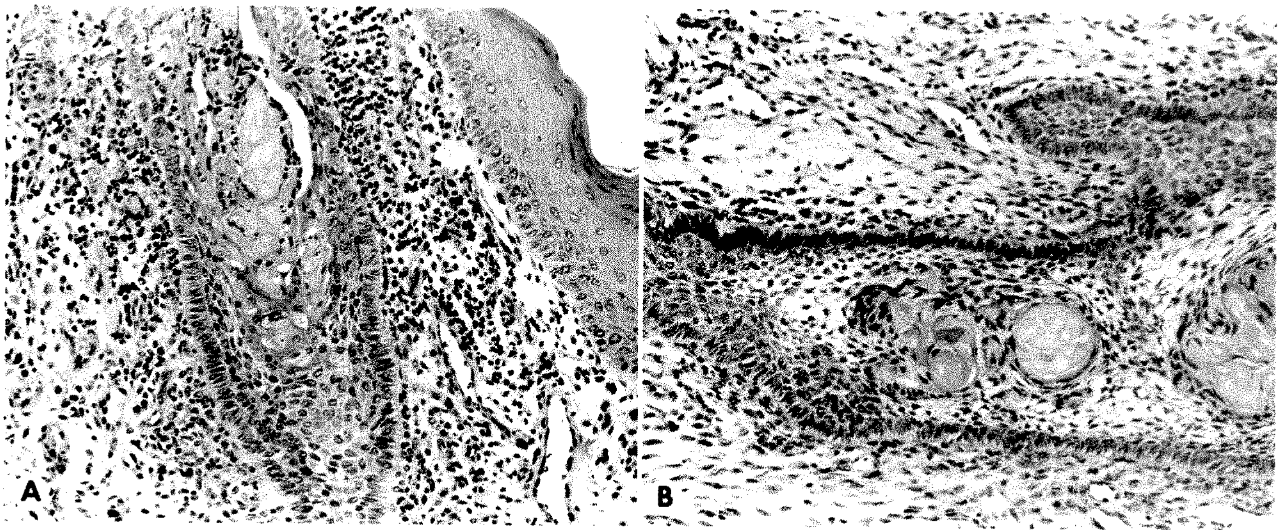

Fig 3. Two histologic fields from surface-originating, peripherally calcifying epithelial odontogenic cyst (H & E). A) Original x160. B) Original x200.

NONAMELOBLASTOMA PERIPHERAL EPITHELIAL ODONTOGENIC TUMORS

The other histologic types of peripheral epithelial odontogentic tumors (Fig 3) are quite rare.[1,5] The few studied do not allow for complete confidence in predicting biologic behavior, but they appear to have low recurrence potential and to be nonaggressive lesions.[1]

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1993 CONFERENCE ON IMPLANTABLE AUDITORY PROSTHESES

The 1993 Conference on Implantable Auditory Prostheses will be held July 11-15, 1993, on the campus of Bryant College in Smithfield, Rhode Island. This is the sixth in a series of biennial research conferences originating with the 1983 Gordon Conference. The meeting will provide a forum for close interaction among scientists in all disciplines relating to the field of cochlear implants. For further information, contact Chris van den Honert, Division of Otolaryngology–Head & Neck Surgery, Box 3550, Duke University Medical Center, Durham, NC 27710; telephone: (919) 684-6099; E-Mail: chx@dukehrl.mc.duke.edu.

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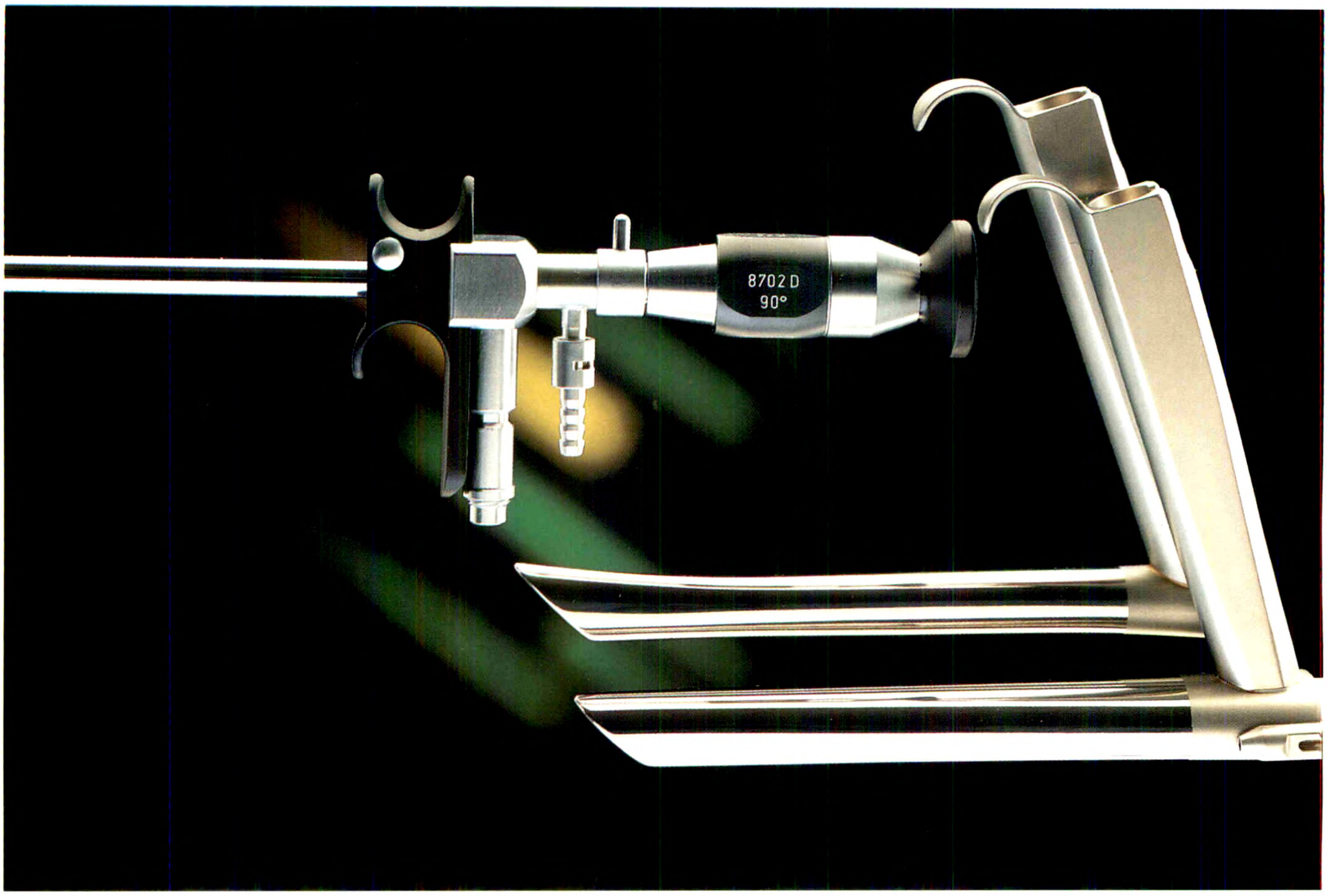

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PARTICLE REPOSITIONING MANEUVER FOR BENIGN PAROXYSMAL POSITIONAL VERTIGO

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Benign paroxysmal positional vertigo is a common, most often self-limited, vestibular end organ disorder that in some cases may be quite disabling. Recent evidence suggests that some, if not most, cases result from free-floating posterior semicircular canal endolymph particles. We postulate that the particle repositioning maneuver displaces these particles from the posterior canal through the common crus into the utricle, where they no longer induce pathologic responses. Our report focuses on 38 consecutive patients treated with this simple bedside technique during a 10-month period. On follow-up, 26 patients (68.4%) were free of disease, 4 (10.5%) were significantly improved, 4 (10.5%) remained unchanged, and 4 (10.5%) were lost to follow-up. Of the 4 patients who remained unchanged, 2 underwent successful posterior semicircular canal occlusions. The direction of the nystagmus during the second stage of the maneuver appears important in predicting the efficacy, with reversal of nystagmus denoting a poor response. These findings provide additional insight into the pathophysiology of this disorder.

KEY WORDS — benign paroxysmal positional vertigo, cupulolithiasis, endolymph.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a common disorder that in one busy vestibular clinic accounted for 17% of new patients.[1] Although Barany first described positional vertigo in 1921, it was in 1952 that Dix and Hallpike[2] first described the specific characteristics of this disorder. These included critical provocative positioning with the affected ear dependent, rotatory nystagmus, brief latency (1 to 5 seconds), limited duration (5 to 30 seconds), reversal on assuming an upright position, and fatigability of the response. To the best of our knowledge after reviewing the literature, positional vertigo with all of these features never arises from a central nervous system disorder.

The cause of BPPV is usually idiopathic; however, it may be seen following head trauma,[3-5] stapes surgery,[6] viral labyrinthitis,[7] or chronic suppurative otitis media.[8] Medical therapy utilizing vestibular suppressants is generally ineffective.[9] Vestibular habituation exercises are effective,[10] but have only recently started to achieve popularity. Surgical intervention is advocated for intractable cases that do not respond to conservative treatment. Operative procedures have progressed from labyrinthectomy and vestibular neurectomy to singular neurectomy and, more recently, posterior semicircular canal occlusion. Singular neurectomy has excellent results in experienced hands[11]; however, it is a technically difficult procedure, performed by few surgeons, with a significant rate of failure and sensorineural hearing loss.[12,13] Posterior semicircular canal occlusion has been shown in animal studies to selectively ablate the function of the posterior canal without adversely affecting the other ipsilateral vestibular receptors[14] or hearing.[15] We recently reported the relative safety and efficacy of this procedure in humans with intractable BPPV.[16,17]

Semont et al[18] reported BPPV treatment results following the "liberatory" maneuver. They achieved 84% and 93% "positive" results after one and two maneuvers, respectively. The procedure involves the patient's lying on the involved side with the head turned 45° up. The patient is then rapidly brought up through the sitting position to lie on the contralateral side with the head turned 45° down. We adopted this maneuver with limited success in late 1990. We found it somewhat cumbersome, however, especially for our elderly population, and have used a modified maneuver since April 1991. Our technique is similar to that taught by Dr John Epley of Portland, Ore, at various instructional courses over the past 10 years. Unlike Dr Epley's technique, ours is performed with no sedation or additional equipment, during our regular outpatient clinic. However, Dr Epley was clearly ahead of his time and deserves full credit for developing the concept of this maneuver.

This report will detail our experience with the technique, which we call the particle repositioning maneuver (PRM). Several interesting findings will provide additional insight into the pathophysiology of this disorder.

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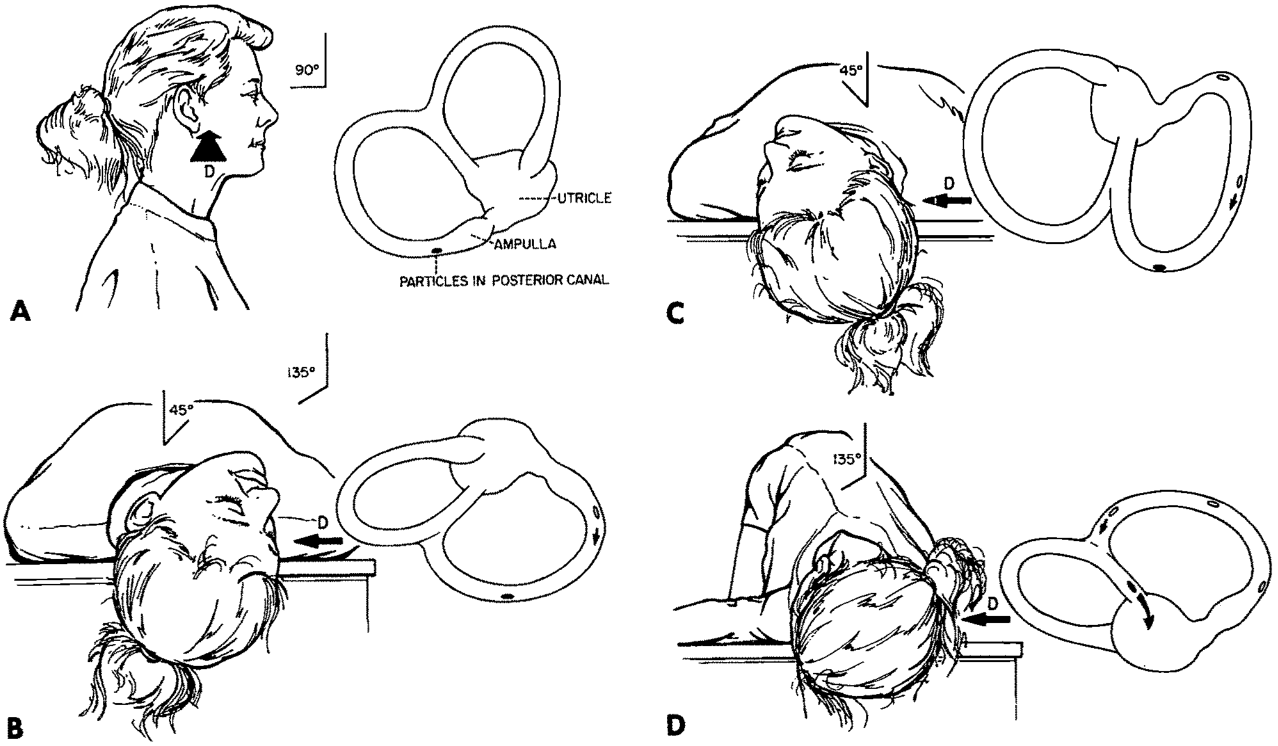

Four positions of particle repositioning maneuver in right ear. Schematic representation of patient and concurrent movement of labyrinth, specifically posterior-superior semicircular canals. D — direction of view of labyrinth, dark oval — new position of particle conglomerate in most dependent part of posterior canal, open oval — previous position. A) Patient seated. B) Patient in Hallpike head position. Particles gravitate in ampullofugal direction, causing counterclockwise rotatory nystagmus (right ear). Position is maintained for 2 to 3 minutes. C) Middle and D) final positions of second stage of maneuver performed in one steady, continuous motion. Particles continue gravitating in ampullofugal direction through common crus into utricle. Eyes are observed for nystagmus response. Position is maintained for 1 to 2 minutes; then patient sits up.

MATERIALS AND METHODS

We studied all consecutive inpatients and outpatients referred to author L.S.P. from January 1, 1991, to February 1, 1992, who ultimately received diagnoses of unilateral or bilateral BPPV. A classic response to the Hallpike maneuver was an absolute requirement for inclusion into the study. All patients were followed up, with no exclusions, and their status was reported as of March 19, 1992. Patients seen prior to September 1991 were reviewed retrospectively, while the remainder were studied prospectively. All patients had a thorough neurotologic history and physical examination, and the vast majority had routine audiometry and electronystagmography. Where appropriate, evoked response audiometry, computed tomography, and magnetic resonance imaging were also performed to rule out concomitant disease. We used the liberatory maneuver during the first 3 months of the study, and the PRM during the last 10 months.

The PRM technique evolved and changed somewhat during the study period. Only one side was treated at any one clinic visit. The current technique begins with the patient seated lengthwise on the examining table (see Figure, A). The Hallpike maneuver is then performed by placing the posterior semicircular canal of the undermost (affected) ear in the earth-vertical axis. The patient then exhibits the classic nystagmus response and is reassured as the vertigo subsides. This position is maintained for 2 to 3 minutes after resolution of the nystagmus. In the second stage, the patient rolls laterally onto the opposite side with the head turned 45° downward. This is performed in a smooth, continuous motion, keeping the neck extended. This serves to rotate the posterior canal 180° in the plane of gravity, theoretically allowing the free-floating particles to continue their relative course through the common crus into the utricle. We elaborate on this concept in Discussion.

While the examiner supports the patient's head, a "secondary" nystagmus response is noted and recorded. A nystagmus response that replicates the initial nystagmus during the Hallpike maneuver is deemed a positive response. Conversely, rotatory nystagmus that changes direction compared to the Hallpike maneuver is considered a reversal nystagmus. There may be no secondary nystagmus, and sometimes the nystagmus direction cannot be determined with certainty. During the retrospective review, cases in which the response to the PRM was not

TABLE 1. DURATION OF BPPV AT TIME OF FIRST TREATMENT (N = 58)

	0-6 mo	*6-12 mo*	*12-24 mo*	*24-60 mo*	*>60 mo*
Completed treatment	21	4	6	12	7
Active treatment	2	0	2	4	0
All patients	23	4	8	16	7

BPPV — benign paroxysmal positional vertigo.

TABLE 2. INITIAL RESULTS OF LIBERATORY MANEUVER (N = 12)

2° Nystagmus Response	*No Evidence of Disease*	*Improved*	*Failure*	*Lost to Follow-up*
+	0	3	0	1
−	2	0	0	1
R	0	0	1*	0
?	3	0	1*	0
Total	5	3	2	2

+ — positive nystagmus, − — no nystagmus, R — reversal nystagmus, ? — unclear or unrecorded.

*Patient underwent successful posterior semicircular canal occlusion.

recorded were also given the last notation (cannot be determined with certainty). After another 1 to 2 minutes the patient sits up and is observed for nystagmus. If it is present, its direction is recorded. With what is felt to be a successful maneuver, one expects to see no nystagmus when the patient returns to the upright position, in contrast to the conventional Hallpike maneuver, in which one usually notes a reversal nystagmus.

Patients were then provided with written information regarding BPPV and instructions to maintain an upright position for 48 hours. They were asked not to lie on the side of the treated ear for a further 7 days as per Semont et al.[18] Most patients were reassessed 3 to 4 weeks later. At this appointment, the patient's subjective response to the treatment was recorded and the Hallpike maneuver repeated. If nystagmus was documented, the PRM was repeated. Treatment stopped once patients became asymptomatic and/or the Hallpike maneuver converted to a negative response.

Patient outcome was recorded as follows. Those with no further positional dizziness and negative Hallpike maneuvers were designated as having no evidence of disease. Those who felt less than 50% improved (subjectively) and had positive Hallpike maneuvers were considered a failure. The "improved" designation was given to those with residual positional vertigo but markedly reduced (subjectively) symptoms, or to those who described vague symptoms of imbalance rather than the positional vertigo they had had previously. The Hallpike maneuver was negative or revealed only a mild, brief response in this last group.

We recommended surgical intervention for patients failing the PRM with a history of symptoms lasting for more than 1 year that were causing significant adverse effects on their life-style. Posterior semicircular canal occlusion was recommended as the procedure of choice.

All patients were asked to complete a short questionnaire concerning the early and long-term results of the PRM. Telephone interviews were conducted with nonresponders.

RESULTS

We treated 58 patients during the 13-month study period, of whom 12 had bilateral disease. Our treatment results are reported according to overall patient outcome, not individual treatment responses. At the time of closing the study, 8 patients were still undergoing active treatment and were excluded from the results except for the demographic data. We therefore report results on 50 patients, of whom the initial 12 underwent the liberatory maneuver and the remaining 38 the PRM. There were 43 women and 15 men with an average age of 59 years, ranging from 26 to 87 years. The duration of BPPV at the time of the first PRM ranged from 5 hours (L.S.P.'s secretary, with a history of recurrent vertigo over the last 4 years) to 35 years, with an average duration of 31.6 months. Table 1 compares the duration of symptoms for patients who have completed their treatment with those who are actively being treated. Approximately half of the patients in each group had symptoms for greater than 1 year.

Of the 58 patients, 46 had idiopathic BPPV; 6 of the cases were posttraumatic, 4 followed viral labyrinthitis or vestibular neuronitis, 1 occurred post-stapedectomy, and 1 followed chronic otitis media. All patients with the last three causes remain free of disease. Of the posttraumatic group (6), 4 remain free of disease. One posttraumatic patient was subjectively improved although she complained of a persistent vague sensation of imbalance following treatment. The Hallpike maneuver was negative on two follow-up assessments. The other patient with posttraumatic BPPV did not return for any of her three scheduled follow-up visits. These last 2 patients were both involved in lawsuits over the injuries they had sustained as a result of the trauma.

Of the 50 patients who have completed treatment, 42 were treated unilaterally, and 8 bilaterally. In the unilateral group (42), 32 had one maneuver visit

TABLE 3. LONG-TERM RESULTS OF LIBERATORY MANEUVER (N = 12)

Initial Result	*No Evidence of Disease*	*Improved*	*Failure*	*Lost to Follow-up*
No evidence of disease	3	2	0	0
Improved	1	2	0	0
Failure	0	0	2*	0
Lost to follow-up	0	1	0	1
Total	4	5	2	1

*Patients underwent successful posterior semicircular canal occlusion.

(defined as one outpatient visit in which one or more unilateral liberatory maneuvers or PRMs were performed), 8 had two, 1 had three, and 1 had five, for an average of 1.3 maneuver visits for unilateral disease. Of the 8 patients undergoing bilateral treatment, 4 had two, 3 had three, and 1 had five maneuver visits, for an average of 2.8.

Hallpike testing revealed bilateral findings at initial presentation in nine patients, more pronounced on one side in seven. Interestingly, four of these seven patients remain free of bilateral disease following a unilateral PRM on the more pronounced side. The other three underwent bilateral PRMs, with two remaining free of disease and one demonstrating no improvement. In the remaining two bilateral patients who presented with symmetric Hallpike responses, one remains free of disease after bilateral PRMs, while the other is significantly improved. Three more patients developed findings in the contralateral ear during follow-up. All remain free of disease following bilateral PRMs. In total, eight patients underwent bilateral treatment. Six remain free of disease, one was improved, and one failed unilaterally.

There were 12 patients with unilateral disease treated solely with the liberatory maneuver (Table 2). On initial follow-up 5 were free of disease, 3 were improved, 2 were lost to short-term follow-up, and 2 were failures. Both failures went on to have successful posterior semicircular canal occlusions. In response to our questionnaire (average follow-up 11 months), 4 consider themselves cured and 5 remain improved. The 2 patients who underwent canal occlusions are considered failures and 1 is still unavailable for follow-up (Table 3).

The short-term results for all 38 patients undergoing the PRM are shown in Table 4. Twenty-six (68.5%) were free of disease, 4 (10.5%) were improved, 4 (10.5%) were failures, and 4 (10.5%) did not return for follow-up. Thus, of the 34 patients who were followed up, 30 had a favorable result (88.2%). In the group of 4 who failed, posterior semicircular canal occlusion was successfully performed on 2. Of the 30 patients with favorable short-term results and long-term follow-up (4 to 13 months, average 6 months), 17 (56.7%) were free of disease, 7 (23.3%) were significantly improved, 5 (16.7%) had recurrences or never improved (failure), and 1 was lost to follow-up (Table 5). Thus, of the 29 patients who were followed up, 24 (82.8%) are pleased with the PRM result.

TABLE 4. INITIAL RESULTS OF PARTICLE REPOSITIONING MANEUVER (N = 38)

2° Nystagmus Response	*No Evidence of Disease*	*Improved*	*Failure*	*Lost to Follow-up*
+	17	2	0	3
–	3	1	1*	0
R	1	0	3*	0
?	5	1	0	1
Total	26 (68.5%)	4 (10.5%)	4 (10.5%)	4 (10.5%)

+ —positive nystagmus, – —no nystagmus, R —reversal nystagmus, ? — unclear or unrecorded.

*One patient underwent successful posterior semicircular canal occlusion.

A further point of interest related to the direction of the secondary nystagmus, summarized for both the liberatory maneuver and the PRM in Table 6. All patients (100%) with positive responses had favorable results. Reversal nystagmus was seen in four of six failures. One other patient with reversal nystagmus reported long-term improvement.

DISCUSSION

The pathophysiology of positional vertigo has been attributed in the past to cervical,[19-21] cerebellar,[22] and vascular[23] disease. However, it is now generally accepted that BPPV is a peripheral vestibular disorder arising from the posterior semicircular canal of the downward ear during the Hallpike maneuver. Experimental stimulation of the posterior ampullary nerve in cats results in clockwise rotatory nystagmus with left-sided stimulation and counterclockwise rotatory nystagmus with right-sided stimulation.[24] Harbert[25] correlated the effect of experimental posterior canal stimulation with the nystagmus seen in BPPV. He concluded that the cupula must undergo utriculofugal deflection during the Hallpike maneuver to produce the observed response.

Initial temporal bone studies of patients with a history of BPPV revealed degeneration of structures supplied by the anterior vestibular artery, with sparing of the posterior semicircular canal but loss of the utricular otolith membrane.[26,27] Hall et al[28] first proposed that movement of endolymphatic densities during positional testing induced an endolymph cur-

TABLE 5. LONG-TERM RESULTS OF PARTICLE REPOSITIONING MANEUVER (N = 30, FOLLOW-UP > 4 MONTHS)

Initial Result	*No Evidence of Disease*	*Improved*	*Failure*	*Lost to Follow-up*
No evidence of disease	13	4	1	0
Improved	2	2	0	0
Failure	0	1	3*	0
Lost to follow-up	2	0	1	1
Total	17	7	5	1
	(56.7%)	(23.3%)	(16.7%)	(3.3%)

*Two patients underwent successful posterior semicircular canal occlusion.

rent and subsequent cupular displacement due to their hydrodynamic drag. Parnes and McClure[29] identified in vivo free-floating posterior canal endolymphatic particles in patients undergoing surgical therapy for BPPV.

The term cupulolithiasis arose from the observation of Schuknecht[30] and Schuknecht and Ruby[31] of basophilic densities adherent to the posterior canal cupula in postmortem temporal bone sections from three individuals known to have premortem BPPV. The adherence of these densities, which were thought to represent displaced otoconia, would result in a density differential between the cupula and the surrounding endolymph, rendering the cupula gravity-sensitive.[32]

Either free-floating endolymph particles or cupulolithiasis would give rise to utriculofugal cupular displacement during the Hallpike maneuver, with an increase in the resting discharge rate of the first-order vestibular neurons resulting in the observed nystagmus response. Therefore, the two conditions may be difficult to differentiate by history or response to routine Hallpike testing.

Prior to the institution of the liberatory maneuver and the PRM, most patients with BPPV were offered no specific initial treatment besides reassurance. Most cases of BPPV are self-limited, spontaneously resolving over 2 to 6 months. During the 13 months of this study, 58 patients with BPPV were seen in a tertiary care otology unit. With an average disease duration of 31.6 months and over half having symptoms for greater than 1 year, the majority of our patients failed to spontaneously recover.

For the purpose of this discussion, it is important to remember that the cupula forms a complete barrier across the ampulla, impermeable to both endolymph and free-floating particles.[33] Therefore, the particles have only one route out of the posterior canal, and that is through the common crus.

TABLE 6. INITIAL RESULTS OF ALL PATIENTS (N = 50)

2° Nystagmus Response	*No Evidence of Disease*	*Improved*	*Failure*	*Lost to Follow-up*
+	17	5	0	4
–	5	1	1*	1
R	1	0	4*	0
?	8	1	1*	1
Total	31	7	6	6
	(62.0%)	(14.0%)	(12.0%)	(12.0%)

+ — positive nystagmus, – — no nystagmus, R — reversal nystagmus, ? — unclear or unrecorded.

*Two patients underwent successful posterior semicircular canal occlusion.

The nature of the secondary nystagmus response offers insight into the pathophysiology of BPPV, and to a great extent predicts the response to the PRM. It is our belief that a positive secondary response is indicative of further passage of free-floating particles in an ampullofugal direction. This leads them through the common crus out of the posterior canal into the utricle, where they no longer cause pathologic responses. The high cure rate supports this concept. Partial responses or improvements likely result from an incomplete reduction of the particle mass.

We postulate that reversal nystagmus during the second stage may occur through one of three possible mechanisms. In one, the particles reverse their direction of movement with an improperly performed maneuver, creating a utriculopetal endolymph current. This is more likely to occur with the liberatory maneuver. Here we rely on inertia for the particles to maintain their position while the patient flips from one lateral position through the sitting position to the other lateral position. However, with the PRM the particles follow the natural curve of the posterior canal as the patient rolls from one side to the other (see Figure, B-D). To ensure this mechanism, the neck should be fully extended during the roll and then flexed upon reaching the second position. Alternatively, the particles may reverse their direction of movement if they meet some obstruction within the membranous duct, for example, in the area of the common crus. It is conceivable that some particles may become adherent to the membrane, occluding the duct enough to prevent passage of other particles but not enough to prevent endolymph flow. Cupulolithiasis is the third possible mechanism underlying reversal nystagmus. The gravitational effect upon a fixed cupular deposit will result in utriculofugal cupular deflection during the Hallpike maneuver (see Figure, B). The position assumed during the second stage of the PRM effectively rotates the posterior canal 180° in the earth-vertical plane (see Figure, D). This would result in utriculopetal cupular displacement and a reversal of the nystagmus response.

Several other findings help support our free-floating particle theory as the underlying mechanism for most cases of BPPV. In several patients with classic histories of BPPV, the Hallpike maneuver failed to initially induce a positive response. In many, a vigorous head shake often elicited a latent response. As well, a few patients required a vigorous head shake during the PRM second stage to evoke a response. The concept of head shaking is not unlike the skull vibrator that Dr John Epley uses with his maneuver. We postulate that in these cases the head shake overcomes the particle conglomerate's inertial force or its minor adherence to the membranous canal wall, allowing for its mobilization.

Free-floating particles may also explain the fatigability of a conventional Hallpike maneuver. Each maneuver likely causes increasing endolymph dispersion of the particle conglomerate. This results in a reduced mass effect with each subsequent maneuver, reducing its degree of hydrodynamic drag and endolymph current. We have noted in several patients that a repeat Hallpike maneuver 30 to 60 minutes after a fatigued response often elicits the same maximal response seen during the initial Hallpike maneuver. Theoretically, the particles have had time to reassemble into the large conglomerate mass within the endolymph of the posterior canal.

Cupulolithiasis or partial obstruction of the posterior canal membranous duct appears to underlie some cases of BPPV, especially those resistant to a well-executed PRM with evidence of reversal secondary nystagmus. However, the vast majority of our patients had a positive response to the PRM; therefore, we feel that free-floating particles are the most common cause of BPPV. The long-term data show that most patients remain asymptomatic for many months following the PRM. We will continue following these patients in the future to determine the long-term efficacy of this technique. However, to date the results of this simple outpatient maneuver are extremely encouraging.

CONCLUSIONS

It would appear that most, and perhaps all cases of BPPV result from free-floating posterior semicircular canal endolymph particles. The PRM is a simple, effective treatment for most patients with BPPV — even those with prolonged intractable symptoms. It is easier to administer than the liberatory maneuver, especially in the elderly, and seems to be more physiologically sound. A positive second-stage nystagmus predicts an excellent result. Reversal nystagmus during the second stage predicts a poor response. Posterior semicircular canal occlusion remains a relatively safe and effective procedure for intractable nonresponders.

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NEW PERSPECTIVES IN OTOLARYNGOLOGY–HEAD AND NECK SURGERY

This international symposium, to be held July 5-8, 1993, at St Thomas's Hospital, London, England, will be sponsored by Harvard Medical School, Beth Israel Hospital–Brigham & Women's Hospital, Guy's and St Thomas's Medical and Dental School, and the Université René Descartes Faculté de Medicine, Necker Enfants Malades, Hopital Laennec. For further information, contact Harvard Medical School, Department of Continuing Medical Education, PO Box 825, Boston, MA 02117; phone (617) 432-1525.

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ESOPHAGEAL STRICTURE FOLLOWING ESOPHAGEAL ATRESIA REPAIR: ENDOSCOPIC ASSESSMENT AND DILATION

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A retrospective review from 1981 to 1986 was made of 51 neonates who were treated for congenital esophageal atresia at the Royal Alexandra Hospital for Children, Sydney, Australia. Thirty of the 51 had primary repair and 15 (50%) developed esophageal stricture requiring one or more dilations. Stricture dilations were performed with open-tube rigid esophagoscopes, rigid telescopes, and Jackson dilators. The number of dilations performed until the patient was asymptomatic ranged from 1 to 12 (mean 4.5). The minimal follow-up time was 4 years. There was one esophageal perforation with full recovery following conservative management. One child died of septicemia caused by continued aspiration of unknown cause. A surprising finding, contrary to other reports, was that stricture formation did not appear to be related to the size of the "gap" found at the time of esophageal repair. Gastroesophageal reflux, however, was an important factor. We conclude that esophageal stricture following repair of tracheoesophageal atresia can be satisfactorily and relatively safely managed by direct vision antegrade endoscopic dilation using graduated dilators, although treatment may be prolonged and repeated. New esophagoscopes and dilators, in graduated sizes and designed for pediatric use, are recommended. The technique of esophageal dilation in infants is described in detail. Pediatric laryngobronchoesophagologists will become more involved in the care of infants born with esophageal atresia with or without tracheoesophageal fistula.

KEY WORDS — endoscopy, esophageal atresia, esophageal dilation, esophageal stricture.

INTRODUCTION

In the absence of other major anomalies the survival rate in infants of all birth weights operated on by primary repair of esophageal atresia with distal tracheosophageal fistula is over 90%.[1-3] Full-term infants without complicating malformations have an almost 100% survival rate. With improved life expectancy the various complications associated with survival have become more widely recognized. Chronic postrepair problems are caused by recurrent fistula, tracheomalacia, gastroesophageal reflux, and esophageal stricture. The incidence of recurrent fistula is generally reported as about 5%.[3] Tracheomalacia occurs to some degree in most infants and unless recognized endoscopically[4] may be misinterpreted as "postoperative pulmonary complications." Symptomatic gastroesophageal reflux has been described in 29% of children after repair of esophageal atresia[5] and is considered to be one of the major predisposing factors in the formation of stricture.

Esophageal stricture following esophageal atresia repair is a common postoperative complication, sometimes treated by the pediatric surgeon and sometimes by the pediatric laryngobronchoesophagologist. This paper reports the endoscopic assessment and the results of dilation in 15 patients with postrepair esophageal stricture. The technique of dilation and new esophagoscopes and dilators designed especially for pediatric use are described in detail. The pediatric otolaryngologist has become more involved in the primary and secondary care of infants born with esophageal atresia with or without tracheoesophageal fistula.

MATERIALS AND METHODS

Between 1981 and 1986 repair of tracheoesophageal fistula with or without esophageal atresia was performed in 51 neonates.

Surgical Technique. Diagnostic endoscopy immediately before thoracotomy for definitive repair was performed in only a few patients in this series. When carried out it confirmed the abnormal anatomy and assessed possible associated malformations such as subglottic stenosis, tracheomalacia, tracheal or bronchial stenosis, upper esophageal segment fistula, or second fistula.[6] Primary retropleural repair of the esophageal atresia with division and oversewing of the distal esophageal fistula was the preferred surgical approach. After single layer closure of the anastomosis using interrupted absorbable sutures, the anastomosis was tested with nasoesophageal instillation of methylene blue. A nasogastric feeding tube was not used because of the possibility it might cause irritation and increase gastroesophageal reflux. A

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postoperative contrast esophagogram was usually performed after 6 weeks and within 6 months, but sooner when indicated by the symptoms. If a stricture was demonstrated and swallowing difficulty was being experienced, the patient underwent endoscopy.

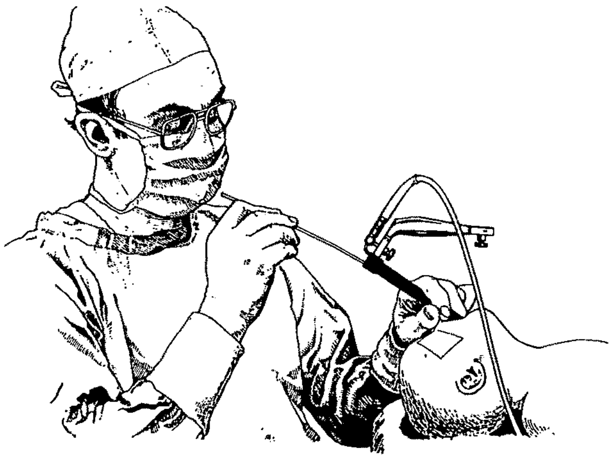

Fig 1. Direct antegrade esophageal dilation under general anesthetic using graduated gum elastic bougies.

Endoscopic Technique. Laryngoscopy and tracheobronchoscopy under general anesthesia[6,7] preceded the esophagoscopy and dilation.[8] The larynx, trachea, and bronchi were examined by using rigid open tube endoscopes and rigid rod lens telescopes[6,8] to assess vocal cord movement, subglottic diameter, the presence and degree of tracheomalacia, the presence of altered anatomy, or other tracheobronchial anomalies, and finally the residual pouch of the fistula was invariably seen as a wide-mouth diverticulum varying in depth up to 15 or 20 mm. It was usually clean and healthy, but sometimes a suture, some granulation tissue, infected secretions, or scarring was seen within it. Tracheomalacia was diagnosed with a rigid telescope, without a bronchoscope in the trachea, during spontaneous respiration general anesthesia according to the criteria outlined by Benjamin,[4] ie, wide posterior membranous wall, cartilage to membranous wall ratio less than the normal ratio of 4.5 to 1, and collapse and partial loss of lumen of the trachea.

Esophagoscopy was performed through a wide-diameter, round lumen, open tube rigid esophagoscope of suitable diameter and length and with bright distal lighting (Karl Storz, Germany; Fig 1). Dilation was under direct vision; that is, the proximal end (ie, toward the eye of the surgeon) of the stricture was visualized directly and dilation was thereafter by feel. The size of the lumen was recorded according to the diameter of the first dilator passed prior to progressive dilation, early in the series with adult Jackson dilators (72 cm long and working length 57 cm) used in increasing sizes. Later in the series the new shorter (43 cm long and working length 33 cm), graduated Jackson-Benjamin pediatric dilators (Karl Storz, Germany) were found to be more convenient and easier to handle. They are preferred and recommended. The dimension of the stricture did not necessarily correspond with the appearance on the contrast esophagogram; swallowing capability was the better indication of the severity of the stricture. Esophagoscopy and dilation was repeated until the esophageal lumen improved and lasting symptomatic relief was obtained. There was a wide variation in the frequency, varying from a single dilation only to a series of dilations, sometimes as often as every 2 weeks.

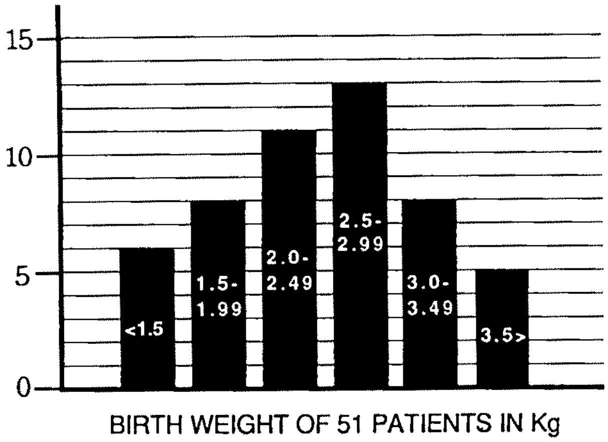

Fig 2. Birth weights of 51 patients with esophageal atresia 1981 through 1986.

RESULTS

Of the 51 patients there were 27 boys and 24 girls. The birth weight ranged between 500 and 4,500 g, with a mean of 2,400 g. The birth weights (low birth weight may be a risk factor[5]) of the 51 children are shown in Fig 2. The anatomic abnormalities followed the usual pattern, with 48 children having esophageal atresia and distal tracheoesophageal fistula. One had a proximal fistula, and two had both proximal and distal fistulas. Thirty patients (59%) had one or more other major congenital anomalies (Table 1). Thirteen died of prematurity, congenital heart disease, or other major associated anomalies. Eight came to esophageal replacement. This left 30 patients who had primary repair of their esophageal atresia; 15 developed esophageal stricture and 15 did not. Stricture was defined on the basis of difficulty swallowing and was confirmed by contrast esophagogram. Fifteen of the 51 children developed esophageal stricture requiring one or more dilations, and these 15 form the basis for this paper.

The time from repair to the first dilation ranged from 1 to 35 months, with a mean of 7.5 months. Seventy-five percent of patients presented by 6 months

TABLE 1. ASSOCIATED CONGENITAL ANOMALIES IN 30 OF 51 CHILDREN WITH TRACHEOESOPHAGEAL FISTULA WITH OR WITHOUT ESOPHAGEAL ATRESIA

Congenital heart disease	14
Musculoskeletal	10
Genitourinary	8
Respiratory tract	8
Gastrointestinal	6
Central nervous system abnormalities	4
VATER	6
CHARGE association	1
Chromosomal	1

TABLE 2. SIZE OF GAP IN 30 CHILDREN WITH PRIMARY REPAIR OF ESOPHAGEAL ATRESIA

	Size of Gap (cm)	*No. of Children*
Anastomotic stricture group (n = 15)	<0.5	3
	0.5-2.0	4
	>2.0	4
	Unspecified	4
Nonstricture group (n = 15)	<0.5	3
	0.5-2.0	5
	>2.0	5
	Unspecified	2

or sooner. Thirteen of the 15 children had slowly progressive dysphagia. Two presented with acute symptoms, 1 with food impaction and 1 with a coin obstructed at the anastomotic stricture site.

During the 6-year period 68 endoscopic esophageal dilations were performed on the 15 children by using the technique of antegrade direct vision open tube esophagoscopy and Jackson or Jackson-Benjamin dilators. The number of dilations required was from 1 to 12 (mean 4.5), and all patients responded satisfactorily to become asymptomatic. The distance between the esophageal segments before surgical repair, ie, the "gap," was similar in both the stricture and the nonstricture groups (Table 2). Eight patients had a postoperative leak at the anastomosis; 4 developed strictures, and 4 did not. Six patients had recurrence of the fistula, of whom 2 developed strictures and both had severe reflux. Gastroesophageal reflux was found in only 2 of the 15 in the nonstricture group, whereas it was in 8 of the 15 patients in the stricture group. Three of these 8 required surgical treatment by fundoplication. All patients had the tracheobronchial tree evaluated by endoscopy[6] on one or more occasions, and 10 of the 15 (67%) had tracheomalacia. One child developed signs and symptoms of perforated esophagus following dilation, but made a full recovery with conservative management. One child died of repeated aspiration of unknown cause leading to septicemia — a death unrelated to endoscopy, esophageal stricture, or dilation.

DISCUSSION

Esophageal stricture following surgical repair of esophageal atresia is a relatively common complication, but the causative factors are uncertain. Louhimo and Lindahl "routinely dilated almost all strictures"[2(p220)] and found only 6 severe strictures (ie, that required resection) in their 300 patients over a 30-year period. Bishop et al had anastomotic strictures requiring more than two dilations in 15% of their patients, and they diagnosed 12 "late"[3(p826)] strictures, ie, those first becoming symptomatic after 1 year of age. The incidence has been reported as high[1] when the gap between esophageal segments is long, but stricture formation in our 15 patients did not appear to be related to the type of anatomic congenital anomaly, as the size of the gap was similar in the stricture and nonstricture patients. Shaul et al had a 20% stricture rate and state, "The incidence of esophageal stricture following primary repair has diminished considerably since the reinstitution of a single layer interrupted end-to-end anastomosis."[5(p1190)]

The technique of surgical repair is standardized in our hospital, so that we cannot speculate on the incidence of stricture according to the type of surgical repair.

Sillen et al[1] found that anastomosis under tension and subsequent leakage predisposed to stricture formation. In our series it is not surprising that four of the eight anastomoses with a postoperative leak were associated with stricture formation. The association of gastroesophageal reflux with stricture formation is well recognized.[9] Gastroesophageal reflux in this series was assessed from the clinical feature of repeated vomiting, a contrast esophagogram, and, in most cases, a pH probe and/or radioactive milk scan. Using these criteria we found a high incidence, 8 of the 15 patients having confirmed reflux. If medical management of reflux is not successful, surgical fundoplication should be considered, although the results are less successful in patients with repaired esophageal atresia[9] than in patients with uncomplicated reflux. As one would expect, there was no evidence of any association between esophageal stricture and tracheomalacia.

Sillen et al[1] defined stricture according to three or more dilations, and not usually on the appearance of the esophagogram. Our diagnosis of a stricture is based on the clinical features of difficulty swallowing, confirmed by contrast esophagogram, and finally verified and calibrated at endoscopy. Most patients present with progressive difficulty swallowing as the

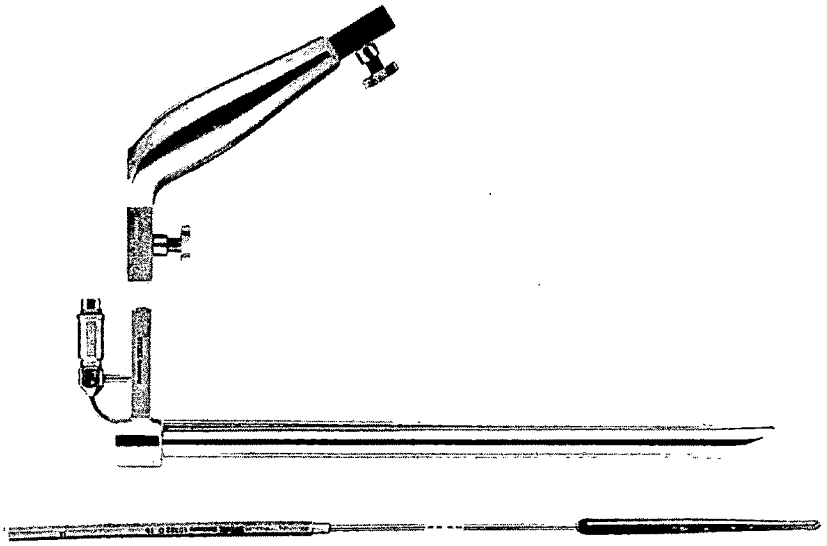

Fig 3. One of set of new esophagoscopes suitable for stricture dilation with (below) one of new shorter gum elastic esophageal dilators ranging in size from 6F to 30F, designed especially for esophageal dilation in infants.

lumen narrows, but a few present with food or foreign body impaction at the stricture site. Estimation of the apparent diameter of the stricture seen on the contrast esophagogram may be unreliable and does not necessarily correlate with the findings at endoscopic examination or the size calibrated with esophageal dilators. Endoscopy employing image magnification with rigid rods lens telescopes is important for complete assessment, including the presence or absence of esophagitis, ulceration, or bleeding. On the other hand, esophagography and videofluoroscopy are essential in demonstrating the dynamics of swallowing and showing the presence and degree of neuromuscular incoordination. A satisfactory contrast study soon after repair does not preclude later stricture formation; one of our patients presented at 35 months. Delayed onset of this nature may indicate the influence of gastroesophageal reflux further affecting the already scarred anastomotic repair site.

When a stricture is forming after surgical anastomosis it is difficult to decide whether dilation should be performed early or late. Some advocate "routine dilations"[2(p220)] if a stenosis is detected at an x-ray study 2 weeks after repair. We have not performed routine esophagoscopy, but we do favor early endoscopic inspection and dilation when a stricture is suspected. It is easier to treat a stricture in the early stages than later, when it is firm and fibrotic. On the other hand, it could be argued that even careful dilation increases the danger of esophageal disruption or even reformation of the fistula. When first seen at esophagoscopy and examined with an appropriate rigid rod lens telescope[8] the stricture may be central and easy to find, may be irregular, may be short or long, may be easy or difficult to dilate, may feel "tight," may bleed a little or a lot, may be pinpoint, and in difficult cases may have a lumen that is difficult to identify and found only at a subsequent endoscopy. A single dilation may be effective for some patients, but most require more than one dilation, the range being 1 to 12 in our series, with a mean of 4.5. The timing and frequency of subsequent dilations is judged for each patient, according to swallowing difficulty, size of the lumen, and the success achieved with each dilation.

It is difficult to describe to what diameter dilation should be carried out, as it is a matter of "feel" and experience. Clearly it would be prudent to stop before there is rupture of the esophageal wall. Traumatic rupture is less likely during dilation of an established stricture, in which previous dilations have caused periesophageal fibrosis, than in an infant having the first dilation after repair of esophageal atresia. Serially larger dilators are passed until the area of the stricture is felt to "give," usually accompanied by a little bleeding. Thereafter, one or more larger dilators are introduced or dilation is continued up to the largest size that will pass through the esophagoscope, eg, a 28F dilator through a 12 x 14-mm esophagoscope in an 18-month-old child.

Minor swallowing problems such as recurrent episodes of dysphagia or impaction of an ingested foreign body may need further dilation. They may be due to the stricture's getting tighter, to motility problems, or to a combination of both.

Recently, a new set of esophagoscopes with bright distal fiberoptic lighting and a new set of shorter pediatric-size Jackson-Benjamin dilators (Fig 3) have become available (Karl Storz, Germany). The set of new Benjamin pediatric esophagoscopes for infants and children range from the smallest, 7 x 8 mm and 22 cm long for neonates, up to one that is 12 x 14 mm and 37 cm long. These open-tube, almost circular, rigid esophagoscopes have bright distal fiberoptic lighting allowing excellent visualization for diagnosis and easier and less traumatic removal of foreign bodies, and they are especially suitable for dilation of strictures. The handle gives a well-balanced feel, and the distal opening is nontraumatic. The new Jackson-Benjamin esophageal bougies are the first made specifically for pediatric use and are recommended for dilation of esophageal strictures in pediatric patients of all ages, but especially in infants. They have a working length of 33 cm (conventional adult bougies have a working length of 57 cm) and are easy to manipulate. The smallest is 6F (2 mm) in diameter, and they increase by 2F sizes to 30F (10 mm). They are made to be used in conjunction with the new esophagoscopes. For dilation above 30F, the longer adult Jackson bougies are used. We do not perform flexible esophagoscopy for strictures, nor are other forms of dilation used.

There is no acceptable definition of an adequate lumen, but it seems satisfactory to judge on the functional swallowing ability of the child, together with the radiographic appearance.[6] We did not find it necessary to leave a string in the lumen of the esophagus in this series. Other difficult, complicated cases, not reported in this series, have required retrograde dilation through a gastrostomy using Tucker's dilators — a technique we find very useful. However, gastrostomy itself may cause a higher incidence of gastroesophageal reflux and thus predispose to stricture. Gastroesophageal reflux appears to be an important factor in the formation of stricture after anastomosis of esophageal atresia. As only three patients had a fundoplication, there were insufficient patients in this study to draw any conclusion about the result of fundoplication in the management of stricture. Other possible factors are the abnormal anatomy (in particular the size of the gap), the technique of surgical repair, the occurrence of a "leak" after repair, and perhaps other unknown factors.

The primary results of surgery for esophageal atresia have improved, and long-term problems are increasingly important. Skilled endoscopy is essential in the care of the patient.[6,8] With complete preoperative assessment by the anesthesiologist and surgeon, and with reasonable care, experience, and attention to detail, anesthesia and endoscopy cause minimal morbidity.

Esophagoscopy and direct vision antegrade bouginage of an esophageal stricture is relatively safe and effective in the treatment of postoperative anastomotic esophageal strictures. Furthermore, endoscopy of the tracheobronchial tree performed at the same time as esophagoscopy allows examination for possible tracheomalacia, examination for suspected recurrent fistula, and assessment of any associated anomalies.[4,6]

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EARLY DIAGNOSIS OF OTOLOGIC WEGENER'S GRANULOMATOSIS USING THE SEROLOGIC MARKER C-ANCA

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Wegener's granulomatosis is a systemic vasculitis that may involve any organ system. Otologic manifestations are common, and can be the presenting complaint. In the past, diagnosis often necessitated the development of characteristic pulmonary or renal disease. The identification of a new serologic marker, cytoplasmic pattern antineutrophil cytoplasmic autoantibody (C-ANCA), allows for the early diagnosis of Wegener's granulomatosis and gives the patient the best chance for remission with cytotoxic therapy. We report two patients with Wegener's granulomatosis who presented with refractory otitis media, one of whom subsequently developed facial nerve paralysis, in which an early diagnosis was facilitated by the use of the C-ANCA test. Otologic manifestations of Wegener's granulomatosis and the basis of the C-ANCA test are discussed.

KEY WORDS — C-ANCA, Wegener's granulomatosis.

INTRODUCTION

First defined as a distinct entity in 1936,[1] Wegener's granulomatosis is characterized by epithelioid necrotizing granuloma and disseminated vasculitis involving small arteries.[2] Although the lung and kidney parenchyma are primarily affected, any organ system can be involved. Approximately one third of patients with Wegener's granulomatosis present with a locoregional form of the disease, which can last months to several years.[3] Once progressing to the classic generalized form, the disease can run a rapidly fatal course if untreated (mean survival 5 months).[4] In the limited locoregional phase, diagnosis can be difficult and often is delayed. Early diagnosis and treatment with cytotoxic agents and steroids has resulted in a high clinical remission rate.[4]

Depending on the series cited, 19% to 45% of patients with Wegener's granulomatosis will have otologic disease at some time during their illness.[2,5,6] The most common otologic findings include serous otitis media, sensorineural hearing loss, and chronic otitis media.[7] In the locoregional disease phase, a patient with Wegener's granulomatosis may present with primarily otologic disease. The ability to diagnose Wegener's granulomatosis in this early stage has been dramatically improved with the identification of a serologic marker.

In 1982 Davies et al[8] described the presence of antineutrophil cytoplasmic autoantibody (ANCA) in association with Wegener's granulomatosis. This serologic marker has since been subdivided into distinct cellular immunofluorescence staining patterns, with cytoplasmic-accentuated staining characteristic of Wegener's granulomatosis.[3] The subtyping of ANCA into C-ANCA (cytoplasmic pattern) and P-ANCA (perinuclear pattern) has improved the specificity of the test for various vasculitides. The antigen of C-ANCA has been identified as the serine protease PR 3 (also known as myeloblastin, p29, and AGP7), which is expressed on the plasma membranes of neutrophils and monocytes.[9] These autoantibodies may play a direct pathogenic role, as ANCA-stimulated neutrophils and monocytes produce superoxide, degranulate, and damage target cells in vitro.[9]

Cytoplasmic pattern ANCA is highly specific for Wegener's granulomatosis, 99% overall, even in patients with other autoimmune or renal diseases.[10] In contrast, the detection of P-ANCA occurs mainly in renal vasculitides.[10] The sensitivity of the C-ANCA test depends on the stage of activity of Wegener's granulomatosis. In active locoregional disease, the sensitivity is 60%, but it rises to 93% with active generalized disease. Cytoplasmic pattern ANCA titers have also been shown to correlate with disease activity.[11] This may later be helpful in gauging therapy.

We report two patients with Wegener's granulomatosis who presented with refractory otitis media, one of whom subsequently developed facial nerve paralysis. The use of the C-ANCA test helped in the early diagnosis of the illness prior to the onset of significant systemic vasculitis, improving the chances for

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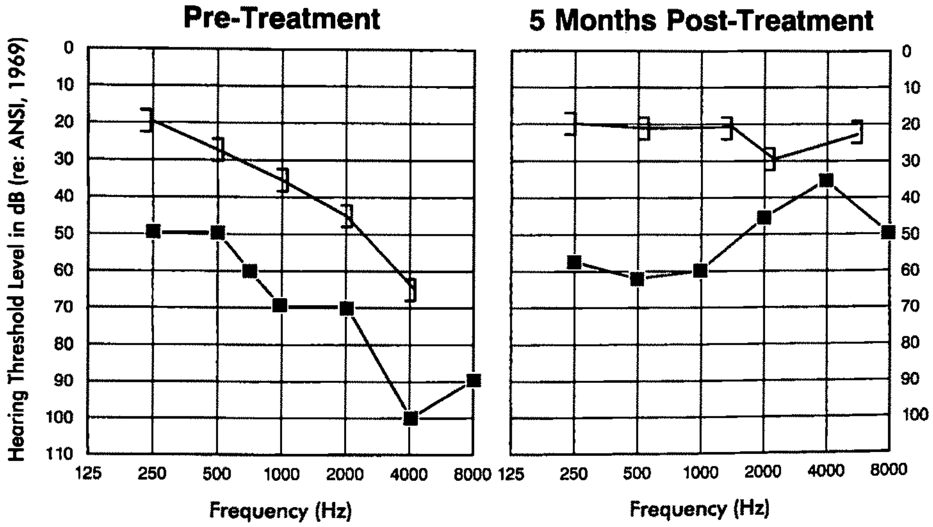

Fig 1. (Case 1) Pretreatment audiogram showing bone conduction pure tone average of 35 dB and conductive hearing loss of additional 20 to 35 dB. Five months posttreatment, audiometric bone conduction pure tone average improved to 23 dB, while conductive component of hearing loss ranged from 10 to 40 dB.

long-term disease remission.

CASE REPORTS

Case 1. This 39-year-old woman, a licensed practical nurse, presented to her local physician with a 2-month history of a painless effusion in her left ear. Despite treatment with multiple courses of antibiotics (ciprofloxacin, cephradine, penicillin, trimethoprim-sulfamethoxazole, and cefaclor) over a 4-week period, she developed purulent otorrhea. She also noted intermittent low-grade temperature elevations (37.7°C), night sweats, morning cough, and diffuse arthralgias during this time. A temporal bone computed tomographic scan was then obtained locally, revealing opacification of the left middle ear cleft and mastoid air cell system, without evidence of bone destruction. Swabs from the ear showed no white blood cells or organisms, and failed to grow organisms in culture. An audiogram revealed a severe down-sloping mixed hearing loss with a 20- to 35-dB conductive component (Fig 1).

Because of an increase in symptoms, myringotomy and tympanostomy tube placement was performed. Repeated cultures from the ear again showed no bacterial, mycobacterial, or fungal organisms. Purulent otorrhea persisted despite Cortisporin otic drops, and she was referred to The University of Iowa Hospitals and Clinics.

When interviewed in our clinic on September 3, 1991, the patient complained of unrelenting purulent otorrhea, severe arthralgias, and fatigue. There was no history of previous ear infections or otologic surgery or of pulmonary, renal, or rheumatologic disease. She had noted recent exposure to tuberculosis at work, and reported that a chest radiograph and a purified protein derivative of tuberculin (PPD) skin test performed approximately 1 year before were normal. She denied any high risk of exposure to the human immunodeficiency virus (HIV). Her medical history was notable only for a long history of smoking cigarettes. Her family history was notable for rheumatoid arthritis in the maternal grandmother and systemic lupus erythematosus in a maternal great uncle.

Physical examination revealed a thin woman with diffuse joint pain on movement. She was afebrile with normal vital signs. Her only abnormal physical findings on head and neck examination were purulent exudate extruding from an anteroinferior central perforation in the left ear and an inflamed tympanic membrane. Examination of the extremities revealed diffuse joint tenderness without effusions. There were no skin lesions.

Significant admission laboratory results included a white blood cell count of 8,000/mm^3, a creatinine count of 0.8 mg/dL, a normal serum electrolyte level, an erythrocyte sedimentation rate of 131 mm/h, an antinuclear antibody titer of less than 1:40, a rheumatoid factor of 47 IU; nonreactive VDRL and fluorescent treponemal antibody tests, a nonreactive HIV-1 test (enzyme-linked immunosorbent assay), and normal urinalysis results. Chest radiographs revealed bilateral apical cavitary opacifications that were not present on radiographs dated January 31, 1989 (Fig 2).

Repeat cultures were taken and the patient was started on mezlocillin and gentamicin intravenously. Gentamicin levels were obtained and therapeutic levels maintained. Repeat computed tomographic scans of the temporal bones were unchanged. Skin PPD plus controls showed anergy. Ear aspirates revealed no acid-fast organisms and grew no other organisms in culture. Serial sputum specimens failed to identify acid-fast organisms. Results of serial

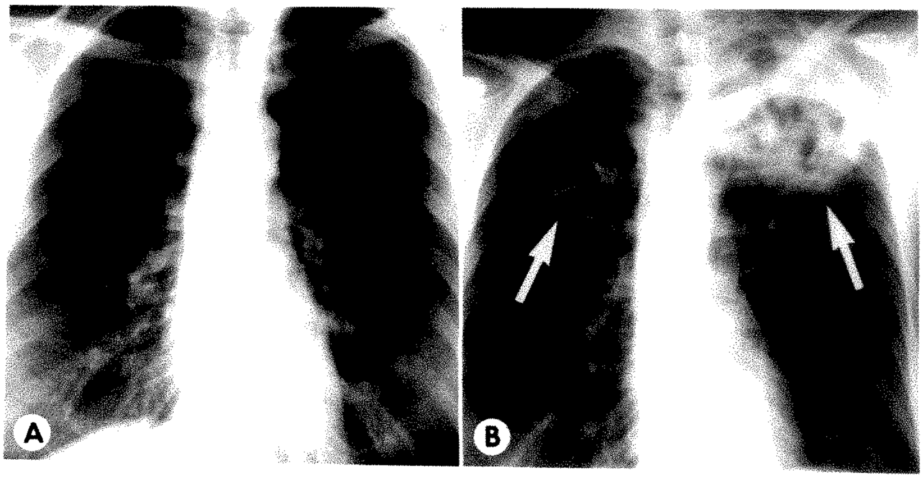

Fig 2. (Case 1) Chest radiographs. A) Normal, taken on January 31, 1989. B) Taken on September 7, 1991. Shows bilateral apical cavitary opacification, left greater than right (arrows).

urinalyses were normal.

The patient was presumptively started on antituberculous therapy. Bronchoalveolar lavage and transbronchial biopsies were then obtained. Again, acid-fast bacilli were not identified. Histopathology of these biopsies showed small necrotizing foci with peripheral palisading histiocytes. The patient was discharged on September 12, 1991, but returned the following day with a complete left seventh nerve paralysis. Examination of the ear revealed purulent fluid in the middle ear on the left, with the anteroinferior perforation occluded by pale middle ear granulation tissue and extrusion of the tympanostomy tube. Myringotomy and tympanostomy tube placement was performed. Again, all cultures were negative. An exploratory tympanotomy was also performed for biopsy of the middle ear mucosa, revealing necrotizing granulomatous inflammation (Fig 3). At that time, the ANCA test returned positive with a titer of 1:320 and demonstrated an accentuated cytoplasmic indirect immunofluorescence pattern. The patient was started on prednisone (15 mg every 4 hours, orally) and cyclophosphamide (2 mg/kg per day, orally). At the time of discharge 7 days later, her arthralgias, fatigue, and appetite were improving.

Since the initiation of treatment 5 months ago, the arthralgias, fevers, and night sweats have resolved. A dry tympanic membrane perforation persists with normal-appearing middle ear mucosa. The patient's facial nerve function has improved to a House-Brackmann grade 3 level of function (Fig 4). Her posttreatment audiogram showed a 10- to 40-dB improvement in the sensorineural component of her left-sided hearing loss (Fig 1).

Case 2. A 52-year-old woman was referred to The University of Iowa Hospitals and Clinics in August 1988 with a 10-week history of a left middle ear effusion and midfacial pain. She also complained of progressive hearing loss in both ears. Her medical history was unremarkable. Physical examination was notable for a retracted left tympanic membrane with a middle ear effusion. The right tympanic membrane

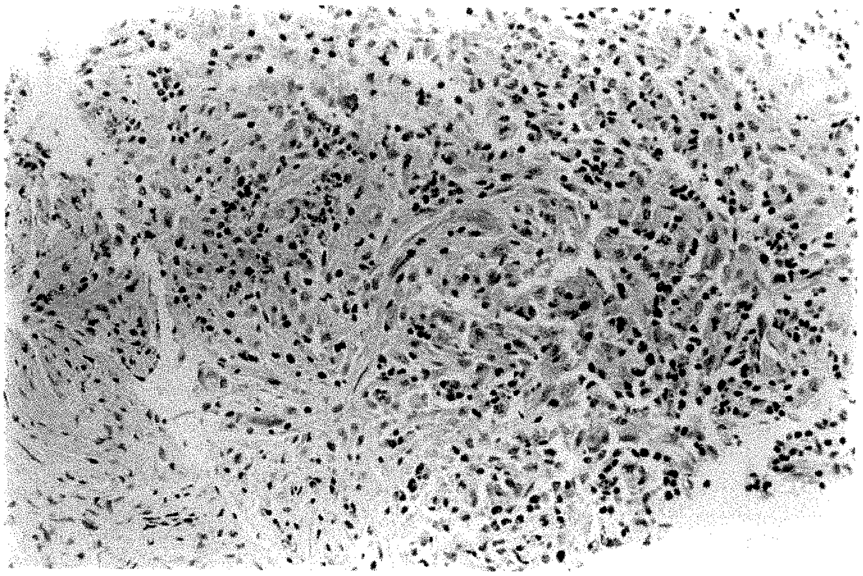

Fig 3. (Case 1) Surgical biopsy of pale hypertrophic middle ear granulation tissue (H & E, original x300). Shows necrotizing foci (center) with peripheral palisading histiocytes.

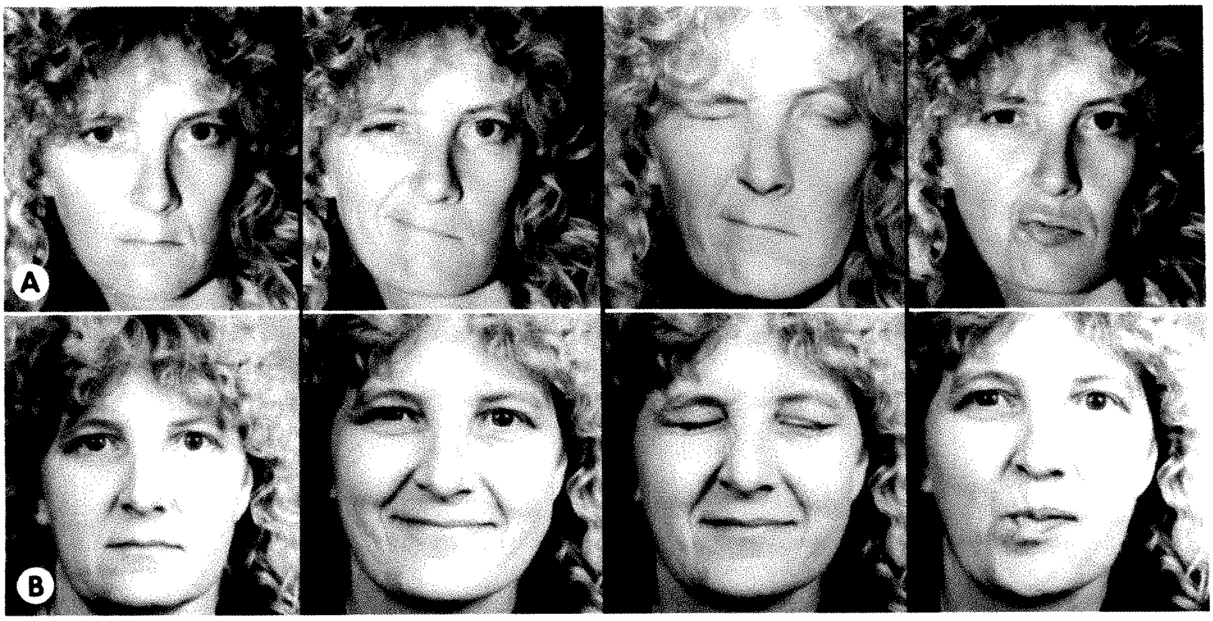

Fig 4. (Case 1) Facial photographs. A) Taken September 13, 1991, showing complete left facial paralysis due to active Wegener's granulomatosis. B) Taken 5 months posttreatment, showing that facial nerve function has returned to level of House-Brackmann grade 3.

was also retracted; however, there was no effusion present. The left middle turbinate had a thickened granular appearance with crusts in both middle meatuses. Her audiogram showed a profound sensorineural hearing loss on the right, and a severe to profound mixed hearing loss on the left. Computed tomography showed opacified mastoid air cells on the left without evidence of bony erosion.

An exploratory tympanotomy was performed and granulation tissue was found in the middle ear on the left. At that time, the ANCA test was found to be positive (>1:32; normal <1:16). Further laboratory results included normal urinalysis results, serum electrolyte level, renal function test results, and complete blood count. The chest radiographs were normal, and radiographs of the hands showed no inflammatory changes. Middle ear cultures grew a few colonies of *Escherichia coli* and *Bacteroides fragilis*. No acid-fast bacilli grew in culture. The patient was then treated with intravenous cyclophosphamide (3 mg/kg per day) and started on oral prednisone (30 mg/d). She responded with a dramatic improvement in her sensorineural hearing levels on the left, ranging from 10 to 35 dB, and resolution of the middle ear effusion.

The patient has since required several admissions to the hospital for recrudescence of her disease, manifested by left middle ear effusions and worsening hearing despite oral cytoxan and prednisone. With each admission and intravenous cyclophosphamide therapy, the middle ear effusions, inflammation, and hearing loss have resolved. Her bone conduction thresholds have remained relatively unchanged in 43 months of follow-up. She has shown no signs of pulmonary or renal abnormalities to date.

DISCUSSION

These patients had a number of otologic findings characteristic of Wegener's granulomatosis. In the study by McCaffrey et al[7] of patients with Wegener's granulomatosis with otologic disease, all 21 patients had a conductive hearing loss, due to serous otitis media, suppurative otitis media, tympanic membrane thickening or perforation, and middle ear granulation tissue. Serous otitis media occurred in 90% of patients with otologic disease, with 33% of these having bilateral findings. Sensorineural hearing loss is the next most common otologic finding, occurring in 43% of patients. The cause of this type of hearing loss is unclear, but possible explanations include vasculitis involving the cochlear vessels, deposition of immune complexes in the cochlea, and granulomatous involvement of the cochlear nerve.[2] Interestingly, the sensorineural hearing loss improves in the majority of cases with appropriate therapy.[5] Chronic otitis or mastoiditis is present in 24%, and is refractory to antibiotic therapy. Surgical intervention does not appear to hasten the course of recovery in these patients.[5]

Facial nerve paralysis occurs in approximately 5% of patients with Wegener's granulomatosis,[7] usually associated with otitis media. In the majority of cases, the facial paralysis has improved with cytotoxic therapy, and our patient with facial nerve involvement has shown significant improvement[5,7,12] (Fig

4). Surgical decompression of the facial nerve has not been shown to improve the outcome of the facial neuropathy.[5,12]

Asymptomatic pulmonary involvement was found in one of our patients (case 1), but there was no evidence of renal disease by renal function tests. That this clinical picture could also be produced by tuberculous otitis media makes empiric immunosuppressive therapy for Wegener's granulomatosis more hazardous.[2] Therefore, every effort should be made to exclude tuberculosis prior to instituting cytotoxic therapy.

Obtaining diagnostic histopathology, especially with locoregional disease, can be difficult. Exploratory tympanotomy with biopsies of the middle ear mucosa may yield nonspecific findings, but was helpful in these two cases to rule out tuberculous involvement of the ear. In other reported cases, invasive procedures such as kidney or lung biopsies have been needed to confirm the diagnosis. These can delay diagnosis until the onset of systemic involvement of the disease, worsening the chances for remission with therapy. The C-ANCA serologic test makes diagnosis possible before systemic signs of vasculitis occur, giving the patient the best chance for long-term clinical remission and avoiding irreversible pulmonary and renal damage. This represents a valuable diagnostic tool for otolaryngologists treating patients with refractory otologic disease and enables this potentially fatal disease process to be diagnosed and treated early in its course.

SUMMARY

Wegener's granulomatosis can affect any organ system, and otologic disease is common. A subset of patients develop limited locoregional disease prior to the onset of classic pulmonary and renal involvement. The ear *may be the only region of involvement* at the time of initial presentation. The otolaryngologist must consider the diagnosis in any patient with otitis media refractory to standard treatment. In this early disease stage, the C-ANCA test is extremely valuable in the diagnosis of Wegener's granulomatosis.

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VALIDATION OF WORLD HEALTH ORGANIZATION GUIDELINES FOR PAIN RELIEF IN HEAD AND NECK CANCER

A PROSPECTIVE STUDY

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In a prospective study of 167 patients with head and neck cancer, we assessed the causes and mechanisms of pain, as well as the efficacy and side effects of analgesic treatment, along World Health Organization (WHO) guidelines. The majority of patients had pain caused by cancer (83%) and/or treatment (28%), 4% had pain due to debility, and 7% had pain unrelated to cancer. Palliative antineoplastic treatment was performed in 32% of patients. Systemic analgesics were administered on 97% of a total of 8,106 treatment days, and coanalgesics or adjuvant drugs on 100%. The treatment proved to be very successful, as severe pain was experienced only during 5% of the observation period. In the absence of serious side effects, the most frequent symptoms observed were insomnia, dysphagia, anorexia, constipation, and nausea. The use of analgesic and adjuvant drugs along WHO guidelines to treat pain in head and neck cancer is highly effective and relatively safe.

KEY WORDS — analgesics, head and neck cancer, pain, World Health Organization guidelines.

INTRODUCTION

Pain is experienced by 40% to 80% of patients suffering from head and neck cancer.[1,2] Difficulties in pain management are common, as many patients suffer from dysphagia or psychosocial problems. The literature on pain management in head and neck cancer consists mostly of case reports and review articles, and there are few epidemiologic or prospective studies available.[3-5]

While invasive methods of treatment are sometimes advanced,[6-11] systemic pharmacotherapy has the advantage of being noninvasive and more freely available. Treatment with analgesics and adjuvant drugs, as recommended by the World Health Organization (WHO),[12,13] has proven to be an effective method of pain relief in various cancers.[14-16] It was the aim of this study to assess the causes and mechanisms of pain and to evaluate the efficacy and side effects of the WHO guidelines for pain relief in head and neck cancer.

METHODS

Patients. Between 1983 and 1989, following informed consent, all patients with head and neck cancer referred to the pain clinic at the Department of Anesthesiology, University of Cologne, for treatment of intractable pain were included in this open prospective study.

Pain Assessment. Pain was assessed on admission on the basis of the patient's history, a standardized questionnaire, physical examination, and review of all available investigations (eg, computed tomography, endoscopy, histodiagnosis).

Sites of pain were marked on a body chart by the patients and evaluated according to the International Association for the Study of Pain classification.[17] Pain intensity was graded by self-assessment, using a six-point verbal rating scale.[18] The pain syndromes were classified by cause and type (mechanism).[3-5,19,20] Causes of pain included 1) pain caused by cancer (compression or infiltration of pain-sensitive structures), 2) pain caused by treatment (consequence of radiotherapy, surgery, or chemotherapy), 3) pain associated with debilitating disease (eg, postherpetic neuralgia or bedsores), and 4) pain unrelated to cancer or treatment (eg, arthritis, migraine, or neuropathy). Pain types included 1) pain of nociceptive origin (stimulation of nociceptors in bones or soft tissues) and 2) pain of neuropathic origin (irritation or injury of nervous tissues, described as projected, dysesthetic [burning], or paroxysmal [stabbing] and

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TABLE 1. ANALGESICS USED IN CANCER PAIN

Type	*Agent*	*Dose (mg/d)*
Nonopioids	Acetaminophen	3,000-6,000
	Flurbiprofen	150-300
	Diclofenac	150-300
	Dipyrone	3,000-6,000
Weak opioids	Codeine	300-600
	Tilidine	300-600
	Tramadol	300-600
Strong opioid	Morphine	30-2,000*

*Dose being titrated against patient's pain.

TABLE 2. COANALGESICS USED IN CANCER PAIN

Type	*Agent*	*Dose (mg/d)*	*Indication*
Antidepressant	Amitriptyline	25-75	Dysesthetic neuropathic pain
Anticonvulsants	Clonazapam	1-4	Stabbing neuropathic pain
	Carbamazepine	200-1,200	
Corticosteroid	Dexamethasone	4-16	Nerve compression
Antibiotic	Metronidazole	500-1,000	Infection
Topical therapy	Bland rinses, local anesthetics, mucosal coating agents		Mucositis

associated with neurologic deficits).

Pain Treatment. Pain treatment was initiated and supervised by our department in cooperation with the patients' specialists and family doctors. The following therapeutic principles, based on WHO guidelines,[12] were applied. Analgesics were selected by a three-step "analgesic ladder"[12,13]: WHO step I (nonopioid analgesics), WHO step II (weak opioids with nonopioid analgesics), and WHO step III (strong opioids with or without nonopioid analgesics). These were administered in an effective dosage (Table 1) and on a regular basis.[12,13] Intervals of administration were usually 4 hours, except in those cases in which sustained-release tablets were used or in which a double dose taken at night allowed an 8-hour interval and facilitated sleep. Medication was preferentially administered by the enteral route.[12,13] Only when coma, severe dysphagia, intractable vomiting, or gastric stasis was present were the medications administered subcutaneously or intravenously.[21]

Coanalgesic drugs were used in certain pain states as indicated (Table 2).[3,5,12,13,22,23] Adjuvants, such as laxatives, antiemetics, histamine 2 receptor antagonists, antacids, antipsychotics (to treat emesis), anxiolytics, or hypnotics, were prescribed to ameliorate coexisting symptoms or side effects of analgesic treatment.[12,13,24]

Palliative anticancer therapy, such as radiotherapy, surgery, or chemotherapy, was administered by specialists whenever appropriate.[3-5,8,12]

Neurolytic blocks or neurosurgical procedures were performed if pain remained intractable on systemic drug therapy either because of inefficacy or because of intolerable side effects.[6-13]

All patients were seen by our department as often as needed, but at least once a week, and the treatment was adapted if necessary. Treatment modalities, pain ratings, and frequency of other symptoms were recorded at each visit and evaluated with a computerized data base system.[25]

Statistics. Age, days of treatment, follow-up intervals, and doses of analgesics are presented as mean ± SD and range. Values are expressed as percentages of either 167 patients or 8,106 treatment days. The Wilcoxon matched-pairs test (statistical package SPSS-PC, SPSS Inc, Chicago, Ill) was used to compare pain ratings prior to treatment and after 1 week of treatment. A value of $p < .05$ was considered significant.

RESULTS

Patient Demographics. We studied 167 patients (116 men and 51 women, mean age 58 ± 11 years, range 18 to 85 years).

Tumor Origin, Staging, and Prior Therapy. The sites of tumor origin (Table 3), tumor stage, and prior therapy were noted. In 65% of the patients, the tumor had advanced to stage T3 or T4, N3, or M1 of the TNM classification.[26] Less advanced stages were found in 16%, and the stage could not be determined in the remaining 19%. Eighty percent of the patients had undergone previous radiotherapy, 63% surgery, and 41% chemotherapy. In 9% of the patients, no anticancer treatment had been supplied.

Pain Assessment. All patients experienced pain in

TABLE 3. SITES OF TUMOR ORIGIN

	Patients (n = 167)	
Site	*No.*	*%*
Nose or paranasal sinuses	3	2
Nasopharynx	14	8
Oral cavity or lips	91	54
Oropharynx	18	11
Salivary glands	7	4
Hypopharynx	17	10
Larynx	21	13
Other sites of head	6	4

Ten patients had two different tumors.

TABLE 4. CAUSE AND TYPE OF PAIN IN HEAD AND NECK CANCER

Cause and Type	*No. of Patients (n = 167)*	*No. of Pain Conditions (n = 310)*
Caused by cancer	138 (83%)	223 (72%)
Soft tissue (nociceptive)	110	140
Bone (nociceptive)	27	31
Neuropathic	48	52
Caused by treatment	47 (28%)	60 (2%)
Soft tissue (nociceptive)	30	35
Bone (nociceptive)	3	3
Neuropathic	17	22
Associated with debilitating disease	6 (4%)	6 (2%)
Soft tissue (nociceptive)	1	1
Bone (nociceptive)	2	2
Neuropathic	2	2
Unknown	1	1
Unrelated to cancer or treatment	11 (7%)	13 (4%)
Soft tissue (nociceptive)	2	2
Bone (nociceptive)	2	3
Neuropathic	3	3
Unknown	5	5
Unknown	6 (4%)	8 (3%)

the region of the mouth, face, or head (81%) and/or the cervical region (40%). Additional pain of the shoulder or upper limbs was noted in 8% of the patients, of the lower back in 7%, of the thoracic region in 5%, and in other locations in 7%. Table 4 reflects the distribution by cause and type of pain. A total of 310 different pain conditions were distributed among 167 patients.

When first seen, 37% of the patients suffered from pain for less than 1 month, 45% for 1 to 6 months, and 18% for more than 6 months. The intensity of pain at admission was graded as severe or worse by 87% of the patients (Fig 1A), even though 94% were taking analgesics at the time. All patients suffered from at least one coexisting symptom, with insomnia, dysphagia, anorexia, and constipation being the most frequent complaints (Table 5).

Pain Treatment. The patients were treated by us for a mean duration of 49 ± 90 days (median 31, range 1 to 579). From a total number of 8,106 treatment days, 52% were on an outpatient and 48% on an inpatient basis. The patients were reassessed at average intervals of 6 ± 5 days (range 1 to 10) as dictated by their clinical condition. Reasons for study termination were therapy continued by family doctor or other hospital (31%), no further therapy necessary (9%), patient lost to follow-up (21%), and death (39%).

The mainstay of therapy was the enteral administration of analgesics on 94% of the treatment days. Parenteral therapy was used on only 3% of the days. On the remaining 3% of the treatment days, other measures, such as radiotherapy alone, were successful in treating pain.

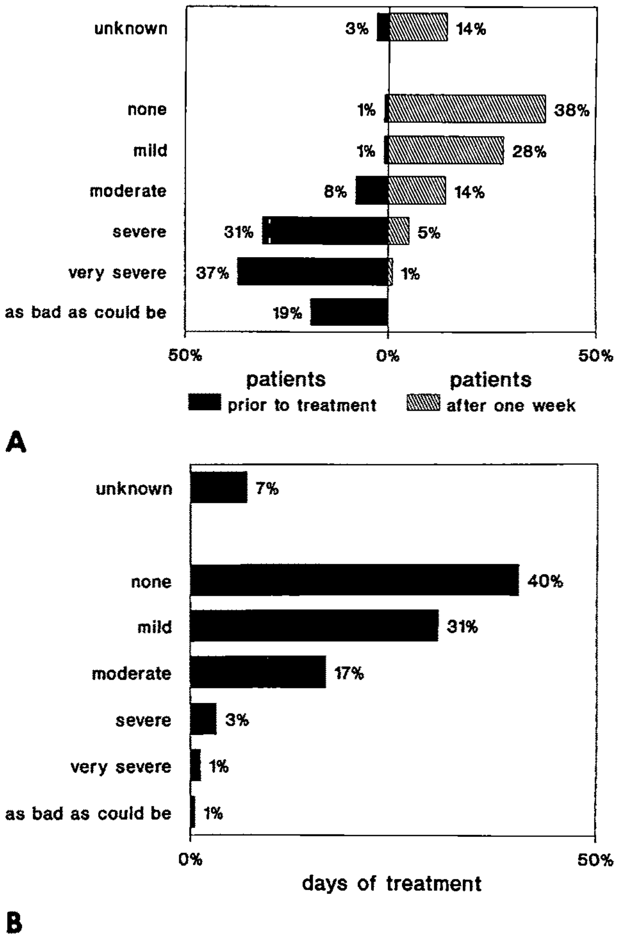

Fig 1. Pain intensity by self-assessment using verbal rating scale. A) In 167 patients before pain treatment and after 1 week of pain treatment. Pain intensity was significantly improved (p < .01). B) During 8,106 days of pain treatment.

Figure 2 represents the distribution of the steps of the analgesic ladder. Nonopioid analgesics were given on 94% of the days, either alone (15%; WHO step I) or in combination with opioids (79%; WHO steps II or III). Dipyrone (metamizole) (4,700 ± 1,100 mg/d orally) was used on 72% of the days, acetaminophen (4,500 ± 1,500 mg/d orally) on 12%, and flurbiprofen (284 ± 44 mg/d orally) or diclofenac sodium (214 ± 73 mg/d orally) on 10% of the days.

Opioids were given on 82% of the days, either alone (3%) or in combination with nonopioids (79%). Tramadol hydrochloride (362 ± 144 mg/d orally) was taken on 21%, tilidine hydrochloride (398 ± 127 mg/d orally) on 7%, codeine (300 ± 0 mg/d orally) on 2%, and morphine on 52% of the treatment days. The average oral morphine dose was 100 ± 97 mg/d (range

TABLE 5. SYMPTOMS BEFORE AND DURING PAIN TREATMENT

	Before		*During*	
Symptoms	*No. of Pts**	*%*	*No. of Days†*	*%*
Insomnia	119	71	2,567	32
Dysphagia	102	61	2,570	32
Anorexia	75	45	2,055	25
Constipation	52	31	1,324	16
Neuropsychologic symptoms	48	29	782	10
Dyspnea	41	25	395	5
Sweating	34	20	151	2
Nausea	28	17	1,165	14
Vomiting	23	14	677	8
Pruritus	11	7	831	10
Gastric pain or ulcer	4	2	578	7

*No. of patients (of total of 167) suffering from symptoms on admission to our pain clinic (prior to initiating pain treatment).

†No. of days (of total of 8,106) during pain treatment on which patients were suffering from symptoms.

30 to 540 mg/d).

The prescription of analgesics had to be modified on average every 18 days, as a result of increasing pain from cancer progression (72%), decreasing pain (18%), increasing side effects (5%), or other reasons (5%).

Coanalgesics or adjuvant drugs were prescribed on all days (Table 6). Anticancer treatment was repeated only in 32% of the cases: radiotherapy in 24 patients, chemotherapy in 17 patients, and surgery in 13 patients. Thermocoagulation of the gasserian ganglion was necessary in 2 patients. Anesthetic blocks were performed in 19 patients.

The pain intensity was significantly improved within 1 week of treatment (Fig 1A). During the course of therapy, patients described their pain as none to moderate on 88% of the days (Fig 1B). On 73% of the treatment days, patients suffered from at least one of the symptoms listed in Table 5.

DISCUSSION

Pain Assessment. Pain assessment is a vital preliminary step toward the satisfactory control of cancer pain.[12] Ignoring this is a major cause of misdiagnosis and inappropriate management.[12]

That all patients were referred to our pain clinic because of intractable pain may explain why the prevalence (100%) and severity (Fig 1A) of pain in this study were higher than reported in other studies.[1,2] Pain other than in the head and neck region was present in 27% of our patients. This was not noted in other studies.

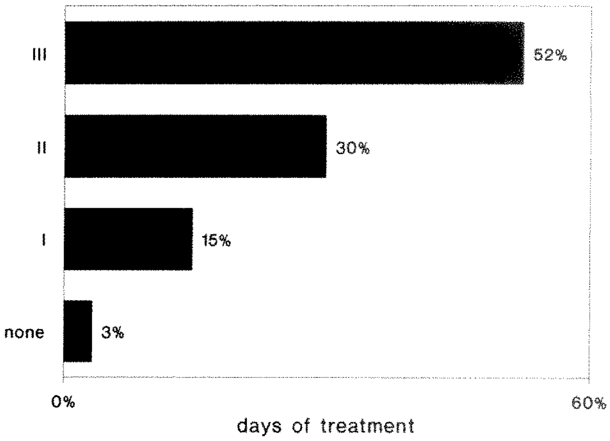

Fig 2. Distribution of steps of World Health Organization analgesic ladder during 8,106 days of pain treatment. None — no analgesics, I — nonopioid analgesics, II — weak opioids and nonopioid analgesics, III — strong opioids with or without nonopioid analgesics.

The mechanisms of pain in head and neck cancer have been described comprehensively,[3-5,8] but have been investigated only in small populations.[4,5] Tumors of the head and neck are located in close proximity to many pain-sensitive structures (mucosa, bone, nerves). As expected, the majority had pain caused by cancer (83%) and/or secondary to the effects of oncologic therapy (28%). This is similar to the report of Vecht et al,[27] who found that 64% of 25 patients with head and neck cancer had cancer-related, 20% therapy-related, and 16% debility-related pain. Greenslade and Portenoy[28] examined 27 patients with head and neck cancer; 19 patients had active cancer causing the pain, and the remaining 8 were considered to be cured of their cancer, so it was concluded that the continued pain was related to the effects of treatment. In cancer of other origins (eg, gastrointestinal tract or respiratory system) pain caused by cancer was seen in 62% to 91% of the patients and pain resulting from oncologic treatment in 4% to 25%.[13,19,29,30]

The majority of our patients' pain conditions (70%) were nociceptive. Neuropathic pain was the second most frequent pain type (25%). These results agree with the findings of Carter et al,[31] in which perineural spread was suspected clinically in 33% and was diagnosed pathologically in 44%. Other studies reported the type of pain in head and neck cancer to be nociceptive in 80% to 85% and/or neuropathic in 20% to 59% of the patients.[27,28] Similar frequencies have been reported in other cancers.[13,19,29,30]

Pain Treatment. The first treatment measure was the prescription of analgesic and coanalgesic drugs on a regular basis to achieve continuous pain relief.[12,13] The use of enteral medication, orally, by nasogastric tube, or via transcutaneous gastrostomy, should be preferred, as it is effective even in severe pain and causes the least restriction of the patient's

TABLE 6. COANALGESICS AND ADJUVANT DRUGS

Drugs	*Days of Pain Treatment (n = 8,106)* No.	%
Coanalgesics		
Anticonvulsants	2,911	36
Corticosteroids	2,164	27
Topical therapy	745	9
Antidepressants	521	6
Antibiotics	308	4
Adjuvants		
Laxatives	3,912	48
Hypnotics	3,834	47
Antiemetics	2,808	35
Antipsychotics	1,491	18
Histamine 2 receptor antagonists	1,116	14
Antacids	575	7
Anxiolytics	167	2

activity.[12,13] Despite the high percentage of dysphagia, oral analgesics could be taken more than 90% of the time. Elixirs or liquid formulations are of major importance in head and neck cancer, as swallowing tablets is often too painful. Sustained-release tablets of morphine or diclofenac, allowing intake intervals of 8 hours, could be used less than 10% of the time. Suppositories have not been found useful for long-term regular treatment (4-hourly), because of poor patient compliance and variable absorption, but may be of importance as a rescue medication in acute situations in which severe vomiting or obstruction of gastrostomy or nasogastric tubes supervenes. Continuous subcutaneous infusion of morphine has been shown to be relatively safe, simple, and effective.[21] In the future, transdermal therapeutic systems for the application of fentanyl may offer an interesting alternative to the parenteral route.[32]

All patients in this study received nonopioid analgesics, unless specially contraindicated. The nonopioids act near the nociceptors (additional central actions are possible) and reduce the pain at the site of origin.[33] In addition, flurbiprofen and diclofenac have an anti-inflammatory effect and have been reported to be effective for bone and soft tissue pain due to inflammation.[3-5,12,13] When nonopioids are combined with opioids, additive analgesic effects may be expected. Combination therapy allows the total dose of morphine to be minimized. Because the dose-related side effects of the nonopioid and opioid analgesics are different and not cumulative, a better risk-benefit ratio can be expected.[12,13,34]

Strong opioids were necessary on more than half of the treatment days. This finding was in keeping with reports on pain treatment for other cancers.[14-16] Many studies have demonstrated that addiction and tolerance are not a clinical problem if correct doses and time intervals for narcotics are adhered to.[12,13,16] Our observations in this study would support this, as no clinical problems with tolerance or addiction were noted. Thus, the use of strong opioids should be determined by the severity of pain and not by the projected life expectancy.

In certain pain types, however, analgesics are less effective,[20] and the use of coanalgesic drugs is extremely important.[3-5,12,13] This is particularly true for neuropathic pain, for which administration of anticonvulsants and/or corticosteroids is useful. Systematic control of other cancer- or analgesics-related symptoms using adjuvants was often a precondition for adequate pain control.[12,13] A comprehensive approach to symptom control was taken, eg, nausea and vomiting (antiemetics, antipsychotics), constipation (laxatives, given prophylactically with strong opioids), insomnia (hypnotics), and gastritis or ulcer (histamine 2 antagonists, given prophylactically to high-risk patients taking flurbiprofen, diclofenac, or corticosteroids). Psychotropic drugs were prescribed mainly in small doses to treat insomnia (hypnotics, antidepressants) or emesis (antipsychotics).[24]

Palliative anticancer treatment can be effective in controlling pain caused by cancer[3-5,8,11] and was performed in 32% of our patients. In the remaining patients, either the oncologic options were already exhausted or no benefit was anticipated from further treatment.

Neurolytic blocks or neurosurgical procedures are reported by several authors to be important methods of pain relief in head and neck cancer.[6,7,9] However, they can produce severe side effects and have a limited duration of action.[3-5,7,8,13,14] In two of our patients with refractory pain in which neurolytic blocks were employed, one had only a short duration of pain relief, and the other developed anesthesia dolorosa. Whenever possible, we preferred the use of drug therapy over destructive procedures. Neuroablative procedures can be of help in selected cases, but should not be the initial treatment of choice.

Emotional state and psychosocial problems play a major role in head and neck cancer. Many patients had preexisting problems with chronic abuse of alcohol and tobacco; in addition, social interactions and emotional expression were disturbed by cancer growth in the face.[3-5,35] One of the most important modalities of our treatment was to spend time listening to the patients, so that special psychologic procedures (eg, hypnosis, relaxation therapy) had to be used only in 12 patients.

Our treatment regimen was very effective, as severe pain was experienced only during 5% of the treatment days. Adjuvant drugs were used liberally and accompanying symptoms were noted quite infrequently. Symptom control was monitored closely, and switching analgesics because of severe side effects was rarely required. No serious side effects were observed.

The efficacy and relative safety of the WHO guidelines for pain relief have already been proven for various other cancers.[14-16] The most comprehensive study to date[14] examined 1,229 patients, 71% of whom were treated adequately with systemic analgesics and coanalgesic drugs. In the remaining 29%, additional neurolytic blocks were performed. The lower percentage of blocks in our patients is probably due to our practice of combining strong opioids with nonopioid analgesics, our use of palliative anticancer treatment whenever possible, and our conservative approach toward invasive treatment.

CONCLUSION

The diagnosis of intractable pain made by the referring physicians was almost always incorrect. Failure to use the WHO guidelines and especially failure to use nonopioid analgesics and coanalgesics[29] was the most common mistake. The use of analgesic and adjuvant drugs is relatively simple, highly effective, and relatively safe and should be available to all patients throughout the world.

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4TH INTERNATIONAL ACADEMIC CONFERENCE IMMUNOBIOLOGY IN OTOLOGY, RHINOLOGY AND LARYNGOLOGY

The 4th international academic conference Immunobiology in Otology, Rhinology and Laryngology will be held in Oita, Japan, April 4-7, 1994. For further information contact Goro Mogi, MD, Dept of Otolaryngology, Oita Medical University, Hasama-machi, Oita 879-55, Japan; telephone 81-975-49-4411 ext 2912 or 2913; fax 81-975-49-0762.

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INTERNATIONAL HEARING AID CONFERENCE GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

An International Hearing Aid Conference will be held June 25-27, 1993, at The University of Iowa, Iowa City. For information on registration and accommodations, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

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CONVERSION DEAFNESS

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Conversion deafness is very rarely encountered among adults. This report will illustrate two cases of this somatoform disorder following different traumatic experiences. It emphasizes the difficulties in establishing the diagnosis and reviews various aspects of treatment.

KEY WORDS — functional deafness, somatoform disorder.

INTRODUCTION

Functional hearing loss can be a common problem in otolaryngologic practice when compensation and medicolegal aspects have a bearing on the case. In functional hearing loss there are audiometric test discrepancies, and apparent organic disease that might account for them has been ruled out.[1]

Conversion disorder is a somatoform disorder defined as a psychologic phenomenon in which there is a loss or change in bodily functioning that results from a psychologic conflict or need. It is most common in women of lower socioeconomic groups. A personality disorder of histrionic type is often present.[2,3]

Serious medical illness and extreme psychologic stress, as well as a preexisting psychopathologic condition, predispose patients to conversion disorder. The American Psychiatric Association[4] criteria for a conversion disorder also include the following. There is a temporal relationship between a psychologic stressor apparently related to a psychologic conflict or need and the initiation or exacerbation of the symptom. The person is not conscious of intentionally producing the symptom. The symptom does not constitute a culturally sanctioned response pattern and after appropriate investigation cannot be explained by a known physical disorder. Finally, the symptom is not limited to pain or to a disturbance in physical functioning.

Although conversion phenomena in otolaryngologic practice are not uncommon and conversion deafness is occasionally encountered in children,[5] it is rarely described among adults.[6,7]

This report will illustrate two cases of conversion

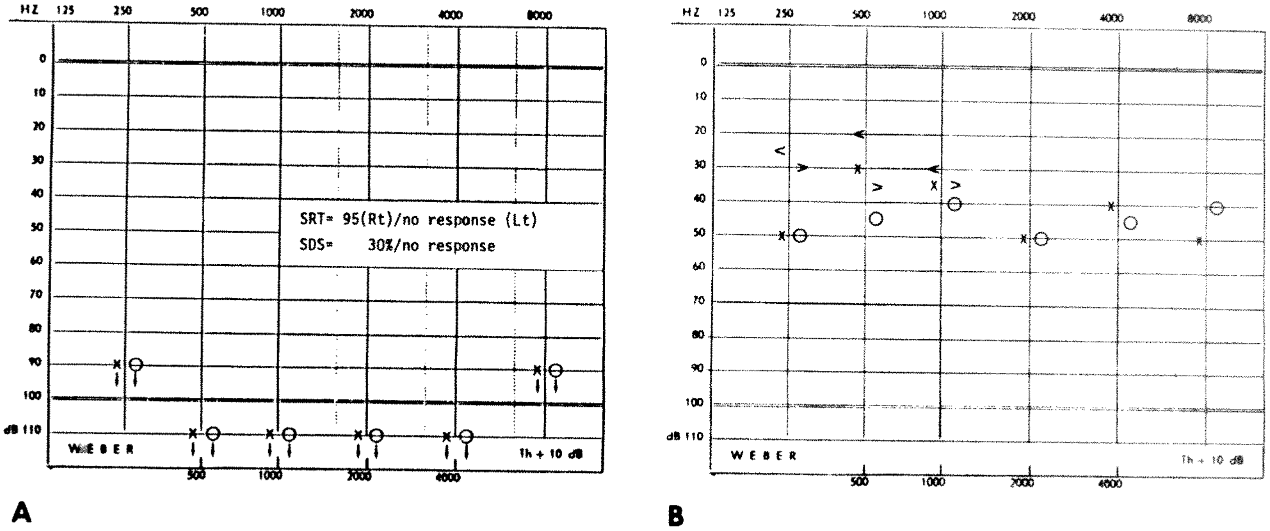

Fig 1. (Case 1) Audiometry. A) On admission, showing bilateral profound deafness. B) On 15th day following injury, revealing bilateral mixed-type hearing loss with low-tone air-bone gap (speech reception threshold at 40 dB on right and 45 dB on left).

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deafness following traumatic experiences. It will emphasize the difficulties in differentiating the disorder from other psychiatric phenomena such as malingering, and will review various aspects of treatment.

CASE REPORTS

Case 1. A 20-year-old soldier suffered from blast trauma and complained of tinnitus and total hearing loss in both ears. Physical examination detected bilateral central perforations of the eardrum that occupied about one third of the tympanic membrane area. Audiometry revealed bilateral deafness (Fig 1A) with speech reception thresholds of 95 dB in the right ear and no response in the left; discrimination scores were 30% and 0%, respectively. The perforations were covered with silk paper patches and the patient was ordered to strict bed rest (assuming inner ear rupture of membranes). The impression of the medical staff, then, was of some discrepancies between the patient's verbal ability to communicate and his hearing impairment; however, repeated pure tone audiometry on the seventh day following trauma remained essentially the same. At the same time repetition of clear characters or half-word responses was noted during the speech reception threshold test, in both ears, and led to the assumption of a functional component. The soldier verbally expressed anger toward his commanding officers, who he felt had neglected him. His affect, in contrast, was indifferent.

Brain stem evoked response audiometry was only partially successful because of the patient's restlessness. Nevertheless, evidence of repeatable waveforms at around 45 dB hearing level (HL) on the left and 60 dB HL on the right were detected (see Table). Functional hearing loss was considered, and indeed, psychiatric consultation revealed an anxious soldier who had been under enormous stress in a combat situation. He reported having had a feeling of impending catastrophe on the day of the injury. Our findings permitted a diagnosis of conversion disorder aggravating the organic insult. The soldier was, by his report, motivated to return to his active duties. The suggested treatment offered combined medical-placebo (slow intravenous drip of glucose 5% solution) and emotional support with daily hearing evaluations. From the 12th day onward, a gradual but consistent improvement was observed (Fig 1B). The perforations closed within 4 weeks on both sides. Moreover, the patient reported feeling better. A 1-year follow-up detected no organic or psychologic abnormalities.

RESULTS OF BRAIN STEM EVOKED RESPONSE AUDIOMETRY IN CASE 1

Decibels Sound Pressure Level	*Side*	*N1*	*N2*	*N3*	*N4*	*N5*	*P5*
100	R	1.95		3.9		5.75	6.3
	L	1.9	2.9	3.8	4.65	5.7	6.0
90	R						
	L						6.3
80	R						
	L						6.5

Results suggest hearing thresholds at 45 dB in left ear and 60 to 65 dB in right ear.

Case 2. In 1963 a 37-year old woman was involved in a minor car accident and 24 hours later complained of bilateral deafness, enabling her to communicate through lipreading only. Her medical history was uneventful. Findings on physical examination were normal and there were no signs of vestibular disturbances. Pure tone and speech audiometry detected no responses in both ears. Vestibular examination revealed no spontaneous or positional nystagmus and the optokinetic and caloric tests were normal. Further elaboration revealed no clear responses during Bekesy audiometry. A functional disorder was postulated because of the surprisingly excellent ability to communicate through lipreading in a patient with acute hearing loss.

A psychiatric examination revealed a reasonably communicating woman (the patient still insisted on communicating through lipreading only) who expressed a marked and long-lasting irritability toward specific noises (eg, yawning, mastication, children's shouting) and who had been recently involved in a minor road accident. Narcoanalysis was suggested for diagnostic as well as therapeutic purposes, and included abreaction that was repeated over a few sessions and revealed the minor present trauma to be associated with a past traumatic experience: the loss of close relatives during the Holocaust, a loss that evoked guilt feelings. A gradual but consistent improvement of hearing up to normal levels was detected through frequent examinations following each analysis (Fig 2). Audiometry performed 20 years later showed essentially the same results as at the last examination (ie, normal).

DISCUSSION

Most cases of sudden deafness lack an apparent cause and are assumed to be related to viral infection, vascular occlusion, ototoxicity, or autoimmune disease. Functional causes have rarely been denoted. Differential diagnosis of functional hearing loss commonly includes malingering, which is considered to be a purposeful, consciously motivated behavior aimed at gaining benefits. In conversion disorder the person is not conscious of intentionally producing the symptom, at least initially.[2]

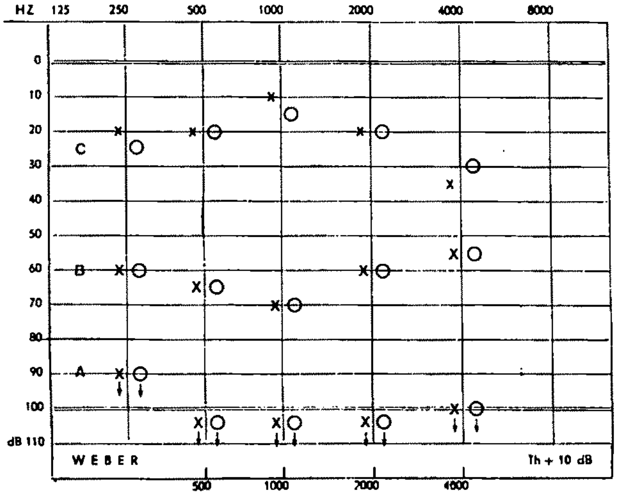

Fig 2. (Case 2) Audiometry. A — on admission (no response in both ears), B — following 5th narcoanalysis (speech reception threshold at 50 dB on right and 55 dB on left), C — following 12th narcoanalysis (speech reception threshold at 20 dB on right and 15 dB on left).

Psychotherapy with these patients is usually aided by hypnosis. It is based on supportive interventions incorporating a prominent element of suggestion. Prompt resolution of symptoms is important in order to prevent chronicity and secondary gains. A thorough observation should, then, be completed in order to verify interpersonal and intrapersonal factors that contributed to the symptoms, and a dynamics-oriented psychotherapeutic approach is required.

Regarding the first case discussed above, since the soldier had not manifested previous abnormal behavior and was eager to get back to duty, the opportunity of a graceful backdown was indicated with no further psychologic analysis. In the second case, the trauma was found to be related to previous events. The target organ chosen to express conversion reaction was related to a long-lasting psychologic and idiosyncratic sensitivity toward noise. Conventional analytically oriented psychotherapy followed the initial diagnosis.

Blast injury affects both middle and inner ear structures, leading mostly to hearing impairment and tinnitus. Profound sensorineural hearing loss, including involvement of the low frequencies, has also been described.[8] Spontaneous improvement of hearing is often described, beginning within a few hours and continuing up to several months after the explosive episode.[8] We assume that during the immediate posttraumatic period our patient (case 1) exhibited combined functional and organic hearing loss. The functional component was reduced within a few days, and spontaneous recovery from the blast trauma continued for over 2 months.

A wide range of examinations is suggested for evaluating functional deafness. Behavioral cues, as noted in the first case, are considered useful and should not be overlooked.[9] Pure tone speech reception threshold discrepancies are quick and easy to obtain. The initial response of the first patient to speech at 95 dB HL with a discrimination score of 30% and no response to pure tones should have raised the suspicion of some functional component, yet in our experience some discrepancies are to be expected at the early stage of a traumatic event.

Modified Bekesy audiometry (lengthened off-time) has been reported to increase the detection rate of a functional cause.[10,11] For bilateral losses, delayed auditory feedback, for tones as well as for speech, seems to be the test of choice.[1] Nevertheless, difficulties are prominent in patients who exhibit bilateral total hearing loss and do not respond to stimulation, such as those described.

The objective physiologic measurements mainly include the acoustic reflex test and brain stem evoked response audiometry, which do have specific limitations. The acoustic reflex test is inappropriate when middle ear problems are encountered, and the establishment of the precise threshold of hearing according to evoked response audiometry requires the patient's cooperation, special techniques, and a well-trained technician.[1]

Functional hearing loss should be considered after other causes are excluded. Various clues may direct the attention toward a conversion phenomenon, including previous episodes of similar characteristics in the patient's family or his or her own history, a previous traumatic experience, a symbolic connection between the trauma and the conversion phenomenon, and a discrepancy between the emotional reaction of the patient and the severity of his disability (*la belle indifference*).

Differentiating between malingering and conversion deafness is challenging. In both, patients may seek medical help, and in both cases the sensitivity of the physician to issues of differential diagnosis is essential.

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SIXTH INTERNATIONAL CONGRESS ON INTERVENTIONAL ULTRASOUND

The Sixth International Congress on Interventional Ultrasound will be held September 7-10, 1993, in Copenhagen, Denmark. For information, contact Christian Nolsøe, Congress Secretary, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

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FUNCTIONAL SINUS TECHNIQUES

An international course on functional sinus techniques will be held in Graz, Austria, September 2-4, 1993. It will be conducted in English. For further information, contact Prof Dr Heinz Stammberger, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; telephone 43-316-385-3448; fax 43-316-385-3425.

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COMPOSITION OF THE OTOSCLEROTIC STAPES: ELECTRON MICROPROBE ANALYSES

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For the first time, otosclerotic stapes have been distinguished from unafflicted controls at a high level of significance by using a spectrum of elements measured by energy-dispersive spectrometer–electron probe microanalyses (EDS/EPMA). Discriminant analyses of the maximum concentration of 13 elements measured at several sites within each of 32 stapes differentiated otosclerotic from unafflicted individuals well above the 95% confidence level. Eight of the 9 control (unafflicted) and 21 of the 23 afflicted stapes were correctly classified. In descending order of contribution to the discriminant function, the elements are Zn > Cr > K > Ca > Si > Mn > Na > Al > Mg > P > Fe > S > Ti. Zinc and chromium account for much of the difference, but discriminant analyses excluding them still distinguish the two groups at the 95% confidence level. These results are consistent with previous reports of high levels of alkaline phosphatase, a zinc-containing enzyme, in afflicted stapes. But the broad spectrum of elements capable of distinguishing otosclerotic stapes warrants study of additional zinc-containing and other metal-containing or metal-activated moieties.

KEY WORDS — alkaline phosphatase, chromium, discriminant analyses, electron microprobe, otosclerosis, stapes, zinc.

INTRODUCTION

The purpose of this research is to determine whether otosclerotic stapes differ in composition from unafflicted controls. The progression of the affliction(s) is poorly defined histologically, compositionally, and physiologically, and this lack undoubtedly has contributed to the failure to determine its (their) cause.

There have been few compositional analyses of otosclerotic stapes. Most have sought to distinguish otosclerotic from unafflicted stapes by concentration of the major elements, calcium (Ca) and phosphorus (P), alone. Few have studied trace or minor element content, and none have suggested that there may be a link between minor element composition and enzymatic activity. Some are contradictory.

Lim and Saunders[1] concluded that otosclerotic lesions may be well or poorly mineralized, that the Ca-P ratio in poorly mineralized lesions is low, and that mineral is distributed unevenly within the lesions. Cramer and Chole[2] found that lesions are variably mineralized. Using radiography and microhardness testing, Roberto et al[3,4] concluded that otosclerotic foci were hypomineralized compared with normal stapes. Lim and Saunders[1] found no correlation between mineralization and sulfur (S) content. Jensen et al[5] detected no differences in mineral content of forearms of otosclerotic and control populations (photon absorptiometry).

Using neutron activation, Soifer et al[6,7] concluded that there were no differences in the levels of Ca, P, iodine (I), magnesium (Mg), copper (Cu), chlorine (Cl), sodium (Na), or zinc (Zn) between either otosclerotic stapes or cortical bone and their controls. They could not explain why their results contrasted with Maurer's,[8,9] in which Ca and P were both less concentrated in otosclerotic stapes. Similarly, Evens and Henkin[10] reported lower mineral content in the malleus and incus of otosclerotic patients. The footplates of 6 of 18 otosclerotic stapes that Sala et al[11] studied showed a low Ca-P ratio and high organic contents, but 5 presented the inverse. Schindler et al[12] reported elevated P and Mg, reduced Ca and silicon (Si), and similar iron (Fe) and aluminum (Al) levels in otosclerotic foci versus control stapes.

Like Soifer et al,[6,7] we presume that compositional changes accompany the histologic progression of the affliction, or that elemental turnover rates differ in otosclerotic and unafflicted stapes. If this hypothesis is correct, then comparison of elemental profiles in otosclerotic stapes, mallei, incudes, and endochondral bone might help determine whether the affliction is systemic or local — a question that remains unanswered[13] despite Valsalva's observation in 1741 of stapedial ankylosis caused by otosclerosis (cited in Maurizi et al[14]). Furthermore, compositional characterization of otosclerotic stapes might help confirm the role of metal-containing moieties such as alkaline phosphatase and lactate dehydrogenase that have been implicated in the disorder.

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REPRINTS — Gary D. Rosenberg, PhD, Geology Department, Indiana University–Purdue University at Indianapolis, 723 W Michigan St, Indianapolis, IN 46202-5132.

TABLE 1. CLASSIFICATION OF 32 STAPES BY DISCRIMINANT ANALYSES OF CONCENTRATION OF 13 ELEMENTS

		Predicted Group		
Experiment	*Actual Group*	*Control*	*Afflicted*	*Total*
Maximum values of 13 elements	Control	8	1	9
	Afflicted	2	21	23
Maximum values of 11 elements (omit Zn and Cr)	Control	7	2	9
	Afflicted	4	19	23
Mean values of 13 elements	Control	7	2	9
	Afflicted	3	20	23

MATERIALS AND METHODS

Stapes bones were surgically removed from patients afflicted with otosclerosis, as a standard procedure in the treatment of the disorder. Control (unafflicted) stapes were surgically removed from patients undergoing a labyrinthectomy or a translabyrinthine removal of an acoustic neuroma. These patients had a profound sensorineural hearing loss, so that their stapes were superfluous. On removal, the stapes were preserved in 90% ethyl alcohol.

Neither the principal author (G.D.R.) nor his microprobe technician knew whether the stapes were from afflicted or control patients until the data were analyzed statistically.

Specimens were mounted on carbon (C) planchets with a drop of epoxy resin. They were coated with spectrographic C in a vacuum evaporator to enhance conductivity.

The composition of the stapes was measured by semi-quantitative energy-dispersive spectrometer–electron probe microanalyses (EDS-EPMA). The microprobe was operated with an accelerating voltage of 15 kV and a specimen current of 0.005 μA. Data were obtained with an ORTEC (HNU) lithium (Li)–drifted Si detector. Specimen counts were accumulated for 200 seconds. The beam diameter was approximately 10 μm. An average of 17 analyses were taken on each specimen.

Analyses were made of the C planchets and of the epoxy resin, as well as of the stapes. Our ORTEC detector will record elements ranging from Na upward, but no signal was ever detected from either the planchet or the epoxy. Thus, the spectra reported here were obtained solely from the stapes.

The elemental spectra that we report should be regarded as "lower bound" estimates of concentration. First, the stapes is porous, like all bone. Second, to avoid contaminating the specimens, we did not grind or polish them flat as is customary for precise quantitative EPMA. Topographic variations produce differential absorption of x-rays (typically, but not always, reducing estimates of concentration), espe-

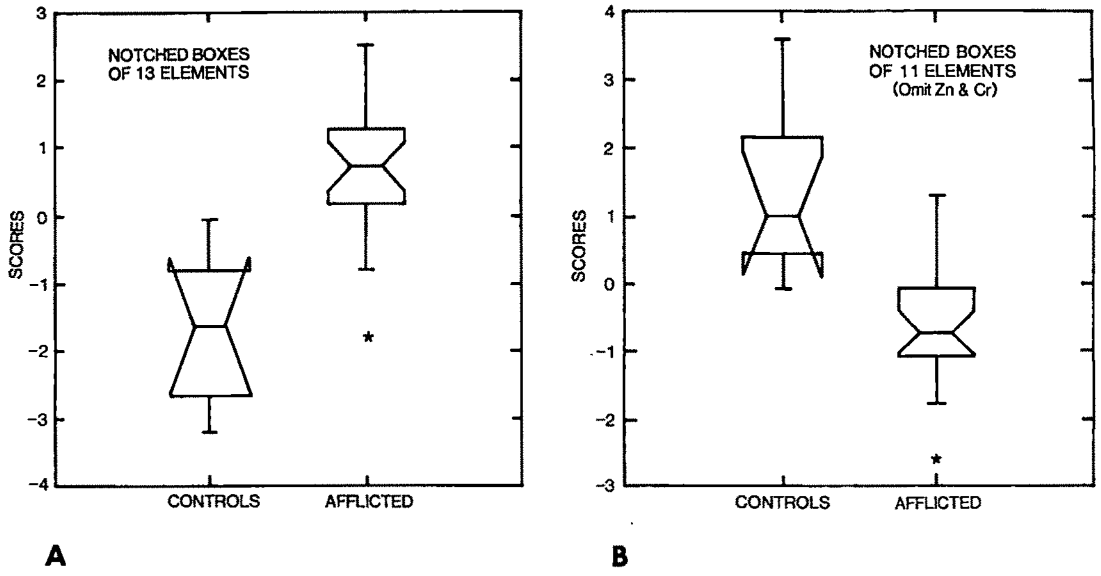

Fig 1. Notched box plots of discriminant function scores (ordinate) for 9 control (unafflicted) and 23 otosclerotic stapes. A) Scores obtained from maximum values of 13 measured cations (Table 1) in each stapes. B) Scores obtained from maximum values of 11 elements (Zn and Cr omitted). A,B) Scores are computed from canonical loadings (Table 2). Boxes are notched and marked with horizontal line at median. They return to full width at upper and lower confidence levels. Note that some of confidence limits are "horns" extending beyond edges ("hinges") of boxes, which are functions of range and distribution of values beyond median. Whiskers (vertical lines) are similar functions. Asterisk denotes extreme value. In A, confidence levels are widely separated, so two groups differ with more than 95% confidence. In B, confidence levels are more nearly equivalent, so that groups differ at slightly greater than 95% level. Note that boxes reverse positions in B because of effect of removal of Zn and Cr.

TABLE 2. CANONICAL LOADINGS AND AVERAGE PERCENT BY WEIGHT OF MAXIMUM VALUES OF 13 ELEMENTS IN CONTROL AND AFFLICTED STAPES

Element	*Canonical Loading*	*Controls*	*Afflicted*
Al	–.135	0.66 ± 1.49	0.31 ± 0.88
Ca	–.193	26.14 ± 4.46	23.18 ± 6.91
Cr	–.338	0.87 ± 0.73	0.34 ± 0.61
Fe	.035	2.82 ± 3.52	3.32 ± 6.43
K	–.242	0.17 ± 0.25	0.06 ± 0.18
Mg	.120	0.19 ± 0.09	0.53 ± 1.38
Mn	.142	0.78 ± 0.64	0.98 ± 0.55
Na	–.140	0.46 ± 1.07	0.22 ± 0.48
P	–.038	22.49 ± 3.02	21.91 ± 6.94
S	.003	3.80 ± 3.60	3.82 ± 1.86
Si	.191	0.21 ± 0.45	2.60 ± 6.03
Ti	.003	0.07 ± 0.10	0.07 ± 0.18
Zn	.365	0.94 ± 1.15	4.08 ± 4.09

cially those of light elements that are also of low energy.

Nevertheless, we do regard the differences in elemental profiles between afflicted and control stapes reported herein as actual and not artifacts of topography or porosity. That there is no difference (at $p \leq .05$, two-tailed *t* test) in Ca-P ratio (1.1 to 1 between the two groups) implies that the effects of topography and porosity are systematic.

Organic-rich calcified tissues do burn beneath the electron beam. However, Rosenberg and Hughes[15] report that relative differences in composition of biominerals are consistent whether analyses are done on C- or Al-coated specimens. Aluminum is a heavier element than C and thus more successfully retards burning, but an Al coating would have precluded analyzing this medically important element within the stapes. Furthermore, we found no apparent differences in composition attributable to duration of exposure to the electron beam (hence to exposure to burning, as some preliminary analyses were done for 100 seconds).

Elemental peak areas within the spectra were compared with peak areas in standard oxides to obtain estimates of concentrations. Hierarchic cluster analyses, canonical discriminant analyses, and box plots, as well as standard *t* tests and F tests, were performed on the data using SYSTAT, a commercially available statistical package. All statistical tests were performed on matrices of 1) the "single maximum" and 2) the "mean maximum" values (averages of all analyses in which the element was detected) in each stapes.

Canonical discriminant analysis is a robust technique not strongly affected by departures from normality in discriminating variables.[16] Here, the variables are functions of elemental concentration. The method attempts to distinguish groups by weighting and linearly combining measured variables to form discriminant functions that maximize group separation.[16] Discriminant function scores are used to calculate the mean location (centroid) of each group, and each specimen is classified on the basis of the proximity to these group means. In this study, a canonical correlation coefficient for an element is a measure of one's ability to distinguish between groups based on that element's concentration. Notched box plots are graphically analogous to a one-way analysis of variance using rank order statistics instead of means.[16,17]

Because the Na_{ka} and Zn_{la} peaks overlap, we were conservative in our identification of Zn. Zinc was deemed to be conclusively identified only if both Zn_{ka} and Zn_{la} peaks were present. Percentage by weight of Zn was always estimated from the Zn_{ka} peak.

RESULTS

Discriminant analyses performed on the "single maximum" value of each element on each stapes correctly classified 8 of the 9 control (unafflicted) and 21 of the 23 afflicted stapes (Table 1). Box plots (Fig 1A) of the discriminant function scores constituted two different populations at well above a 95% confidence level. Absolute values of the canonical loadings (Table 2) indicated the contribution of the elements to the discriminant analysis in descending order of their importance: Zn > chromium (Cr) > potassium (K) > Ca > Si > Mn > Na > Al > Mg > P > Fe > S > titanium (Ti). The signs of the canonical loadings (Table 2) indicated that high values of seven elements are more common in afflicted stapes (ie, positive loadings accounted for the positive median score of the afflicted population on Fig 1): Fe, Mg, Mn, S, Si, Ti, Zn. Six elements tended to be more concentrated in the controls (accounting for the negative median score of the control population in Fig 1A): Al, Ca, Cr, K, Na, P. Two-tailed *t* tests distinguished only Zn levels (at $p \leq .01$) between the two groups. There was no significant difference in Ca-P ratios between the two groups (two-tailed *t* test, Ca-P ratio 1.1 to 1). Omission of Cr and Zn from the discriminant analysis nevertheless permitted the correct classification of 7 of the 9 controls and 19 of the 23 afflicted specimens (Table 1). Box plots (Fig 1B) of the consequent discriminant function scores differed at slightly greater than the 95% confidence level.

Discriminant analyses of the "mean maximum" levels of all elements correctly classified 7 of the 9 controls (Table 1) and 20 of the 23 afflicted specimens. Box plots of their scores (not shown) also

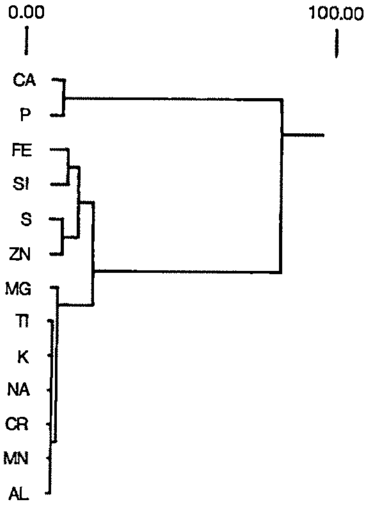

Fig 2. Hierarchic cluster analysis (euclidean distances and Ward's minimum variance method of linkage) using maximum concentration of 13 elements in all stapes. Elements behaving similarly in discriminant function are clustered by short lines. Ca and P; Fe and Si; Zn and S; and Al, Ti, K, Na, Cr, Mn, and Mg constitute four clusters. Zn and S are most closely related to Fe and Si.

differed at well above the 95% confidence level. Box plots omitting Cr and Zn differed at slightly less than the 95% confidence level (not shown).

A hierarchic cluster analysis (Fig 2) of maximum values indicated that Fe and Si, Zn and S, Ca and P, and the remaining elements constituted four groups, each of whose members played similar roles in the discriminant function. The first two groups were most closely clustered with the remaining elements.

There was a highly significant sex-related difference in composition that will be reported elsewhere.

DISCUSSION

Discriminant analyses of 13 cations have successfully distinguished otosclerotic from unafflicted stapes at a high level of confidence. The low Ca-P ratio in both otosclerotic and afflicted stapes indicates that hypomineralization per se does not distinguish the two groups. Zinc and Cr have the greatest effect on the discriminant function, but even without them, the 11 other elements together contrast the groups.

There is some question whether the effects of otosclerosis are restricted to histologically defined foci, localized especially within the stapediovestibular joint, or whether they are more generalized across the entire stapes.[5,13] Because our discriminant functions are derived from measurements made across the entire stapes, and not simply from those within the footplate, our results support the latter alternative.

Davis[18] has stated that the fundamental problem of otosclerosis is to account for the production of new, woven bone in the otic capsule. The tendency of Si, Mg, and S to be more concentrated in otosclerotic stapes is consistent with this scenario, for these elements are known to be enriched during the initiation of osteogenesis.[19-23]

The minor elements also suggest that alkaline phosphatase may be involved in the causation of the affliction. Both Zn^{+2} and Mg^{+2} are functional ions in alkaline phosphatase,[24] with Zn^{+2} constituting approximately 0.20% by weight of the enzyme.[25] We note that both Zn^{+2} and Mg^{+2} tend to be more concentrated in the afflicted stapes studied here.

Evidence for involvement of the enzyme has been contradictory. The activity of the enzyme has been reported to be elevated in the middle ear mucosa and surrounding blood vessels, in the ground substance of otosclerotic foci, and in the perilymph of otosclerotic patients.[6,7,26-29] In contrast, Maurer[8] reported reduced alkaline phosphatase activity in afflicted ears. Chevance et al[28] reported that alkaline phosphatase activity increased during the initial period of lysis, was maximum just before the onset of the reconstructive period, and declined abruptly when calcification of the matrix started. Soifer et al[6,7] and Jensen et al[5] found no difference in serum alkaline phosphatase between controls and otosclerotic groups. Moreover, Zn^{+2} is known to be concentrated in areas of bone undergoing osteogenesis[30] or fracture healing.[31] Dietary Zn deficiency depressed alkaline phosphatase activity in bone,[32] whereas an excess increased activity, inhibited calcification, and induced osteomalacia in embryonic chick femur.[33]

Like Chevance et al[28] and Thalmann et al,[13] we cannot rule out the possibility that other enzymes or metal-containing moieties are involved in otosclerosis. Alkaline phosphatase is a polyfunctional enzyme in both mineralizing and nonmineralizing tissues,[24] so its elevated activity in otosclerotic tissues may be only secondarily related to the pathogenesis. Furthermore, many of the elements analyzed here are found in other enzymes, or have been implicated in their activation. Both Zn^{+2} and Cr^{+3} are involved in the activation of insulin,[34,35] and Zn^{+2} is present in carbonic anhydrase, which is found in the wall of the labyrinth.[36] It is also present in collagenase and lactate dehydrogenase, both of which figure into enzymatic theories of the cause of the disorder,[37] although it must be noted that lactate dehydrogenase activity has been found to be lower in otosclerotic stapes.[38] Parathyroid hormone in rats is known to cause elevated Zn accumulation in soft tissues and bone.[39]

Dietary Zn deficiency may alter sulfate metabolism and reduce S content of bone.[40] Although Table 2 shows a relatively high positive canonical correlation coefficient for Zn, and only a slightly positive one for S, the hierarchic cluster analysis (Fig 2) reveals that both elements behave similarly in the discriminant function. Thus, a dietary connection with otosclerosis might be worth pursuing. Alternatively, a more complex relationship between Zn on the one hand and sulfate-hexosamine ratios on the other may be indicated, given the finding by Riberi et al[41] that the latter ratio distinguishes otosclerotic bone.

Finally, Yoo et al[42] have considered the possibility that otosclerosis is a case of collagen autoimmunity initiated by viral infection and that interleukin-1 contributes to the damage of cartilage by inducing release of metalloproteinases.

In conclusion, our results warrant further attempts to correlate composition of otosclerotic stapes with activities of various enzymes in an effort to better define the progression of the affliction and determine whether the disorder is systemic or localized.

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NEURO-OTOLOGIC ABNORMALITIES IN MYELOPATHY ASSOCIATED WITH HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1

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Auditory testing (pure tone audiometry, auditory brain stem response), and vestibular tests (eye tracking test, optokinetic pattern test, and caloric test) were performed to define neuro-otologic abnormalities in myelopathy associated with human T-cell lymphotropic virus type 1. Of the eight patients tested, seven showed sensorineural hearing loss and one showed mixed hearing loss on pure tone audiometry. The auditory brain stem responses of five patients showed increases of the I-III and I-V interpeak latencies. Two patients showed fast superimposed saccadic movements on the smooth pursuit test, and one other patient showed canal paresis on the caloric test. These findings suggest both the presence of neuro-otologic abnormality and involvement of the brain stem in myelopathy associated with human T-cell lymphotropic virus type 1.

KEY WORDS — caloric test, eye tracking test, human T-cell lymphotropic virus type 1, myelopathy, optokinetic pattern test, pure tone audiometry.

INTRODUCTION

Since it was first recognized by Osame et al,[1] many cases of myelopathy associated with a high antibody titer against human T-cell lymphotropic virus type 1 (HTLV-1) have been reported in Japan. The clinical picture of this entity is characterized by slowly progressive spastic paraparesis.[2]

In HTLV-1–associated myelopathy (HAM) patients, pyramidal signs and sensory and sphincter impairment appear as major symptoms, while sensorineural hearing loss[3] and disturbances of eye movement[4] occur as minor symptoms. We performed pure tone audiometry, auditory brain stem response testing, a smooth pursuit test, an optokinetic pattern test, and a caloric test to detect neuro-otologic abnormalities in HAM patients.

PATIENTS

The subjects were eight HAM patients (three men and five women) whose ages ranged from 35 to 74 years (mean age 57.4 years). Illness duration ranged from 9 months to 31 years. All eight patients suffered from progressive spastic paraparesis with high antibody titers against HTLV-1 in serum and cerebrospinal fluid. The serum antibody titer ranged from 32x to 4,096x, and the cerebrospinal fluid antibody titer from 32x to 8,192x, as determined by the precipitation-agglutination method.

Regarding otologic symptoms, one patient complained of hearing impairment and two complained of vertigo as initial symptoms. One of the two patients who complained of vertigo had first-degree rotatory positional nystagmus. No other evidence of cranial nerve deficiency was noted. None of the patients showed evidence of otitis media.

METHODS

Pure Tone Audiometry. Pure tone thresholds were measured in each patient by air conduction at 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz, and by bone conduction at 0.25, 0.5, 1, 2, and 4 kHz.

Auditory Brain Stem Response. Auditory brain stem response was examined in both ears in five patients. Stimulation consisted of 3,000-Hz single sine wave clicks of 21.1/s, at an intensity of 70 dB normal hearing level, delivered from a TDH-39 earphone. The ages of these patients ranged from 35 to 65 years. Silver-cup electrodes were attached to the upper forehead (active), the mastoid of the tested ear (reference), and the lower forehead (ground). The contact resistance was 3,000 Ω or less. The filter bandpass was 30 to 3,000 Hz, and all responses were recorded at least twice by a Bio-Logic Brain Atlas III system. The limit of the normal range of peak and interpeak latencies was set to a mean of ±3 SD of the normal values in our laboratory.

Electronystagmography. Eye movements were recorded by AC electronystagmography using silver–silver chloride electrodes attached bilaterally to the canthi. Eye movements of 10° were set at 10 mm

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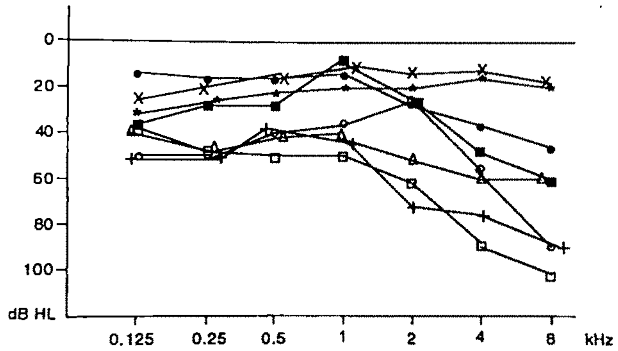

Fig 1. Mean right and left ear air conduction thresholds for each of eight patients. All patients showed variable hearing loss. Average air conduction threshold level at 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz ranges from 27.5 to 58.4 dB hearing level (HL).

on the recording paper. The smooth pursuit test and optokinetic pattern test were carried out in all eight patients. The stimulus for the smooth pursuit test was a small luminous target that moved in a pendulum manner horizontally ±10° from midposition at 0.3 Hz. Optokinetic stimulation was induced by an electrically rotating drum; maximum stimulation was 160°/s. When the maximum level of slow phase velocity was more than 60°/s, and the numbers of nystagmus for 1 second were more than 2, we judged the response as normal.

Caloric stimulation was performed as follows. The external ear canal was irrigated with 20 mL of 22°C water for 10 seconds. The patients were in bed in the supine position with the head elevated 30° from horizontal, and they were instructed to keep their eyes open; the testing was done in darkness. Eye movements were recorded by electronystagmography. We judged the response as showing canal paresis when the maximum velocity of the slow phase was less than 10°/s.

RESULTS

Pure Tone Audiometry. Figure 1 shows the mean right and left air conduction thresholds for each patient. The average air conduction threshold level at 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz ranged from 27.5 to 58.4 dB hearing level. The average air-bone gap ranged from 5 to 12.5 dB (Table 1), indicating sensorineural hearing loss. One of the patients, whose air-bone gap was 25 dB at 0.25 kHz and 15 dB at 0.5 kHz, showed mixed hearing loss, with no evidence of otitis media or otosclerosis.

Of the eight patients, five showed symmetric thresholds in the right and left ears, and three showed asymmetric thresholds at 4 and 8 kHz.

Auditory Brain Stem Response. Five of the eight patients were tested for auditory brain stem response.

TABLE 1. AIR CONDUCTION THRESHOLDS AND AIR-BONE GAPS FOR EACH PATIENT

Frequency (kHz)	*Air Conduction (dB hearing level; n = 18)* Mean	SD	*Air-Bone Gap (dB)* Mean	SD
0.125	36.9	13.1		
0.25	35.9	14.3	7.2	8.0
0.5	32.8	13.0	6.7	8.4
1	27.5	17.0	5.0	6.3
2	37.8	20.7	5.6	6.6
4	47.8	27.9	12.5	15.2
8	58.4	29.4		

The thresholds of these five patients were symmetric, and the average right and left air conduction thresholds at 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz ranged from 25.5 to 43.5 dB hearing level. The average air-bone gaps ranged from 2.5 to 5.5 dB, indicating no conductive hearing loss. Auditory brain stem response components of at least waves I, III, and V were recorded in all tested ears. Table 2 shows the mean peak latencies of waves I, III, and V and the interpeak latencies of waves I-III, III-V, and I-V. Increases occurred predominantly in the peak latencies of waves III and V and in the interpeak latencies of waves I-III and I-V. These increases were statistically significant, as determined by Student's *t* test. Increases of wave III peak latencies and I-III interpeak latencies were observed in six ears, and increases of wave V peak latencies and I-V interpeak latencies were observed in five ears of three patients. There was no significant difference in interaural latency in any case.

Electronystagmography and Caloric Test. Two of the eight patients showed fast superimposed saccadic movements to a sinusoidal curve on the smooth pursuit test (Fig 2). Those were small and fast saccades of 2/s to 3/s with a velocity of over 300°/s.

All eight patients showed symmetric patterns on the optokinetic pattern test, and none showed a decrease of slow phase maximum velocity, or a decrease of numbers of nystagmus.

Caloric stimulation with 20 mL of 22°C water was given bilaterally and separately to all patients. One patient showed unilateral canal paresis.

DISCUSSION

The clinical picture of HAM is characterized by slowly progressive spastic paraparesis, urinary frequency, and sensory impairment. Some HAM patients also show neuro-otologic abnormalities, including hearing impairment and disturbances of eye movement. In a previous report, Kakigi et al[5] observed that 5 of 16 patients had mixed hearing loss, unilaterally in 4 cases and bilaterally in 1 case. No

TABLE 2. PATIENT AND CONTROL AUDITORY BRAIN STEM RESPONSE RESULTS

	Controls (n = 30)		*Patients (n = 10)*	
	Mean	*3 SD*	*Mean*	*3 SD*
Peak latencies				
I	1.59	0.11	1.75*	0.20
III	3.66	0.19	4.25†	0.27
V	5.48	0.26	6.21†	0.22
Interpeak latencies				
I-III	2.07	0.15	2.52†	0.28
III-V	1.82	0.15	1.94	0.15
I-V	3.89	0.20	4.64†	0.21

$^*p < .05$.
$^\dagger p < .01$.

component of the auditory brain stem response could be identified in the affected ears. These investigators also observed that the peak latencies of waves I to V and interpeak latencies I-V and III-V were normal in the unaffected ears.

It has been reported that some patients with tropical spastic paraparesis,[6] which is a disease similar to HAM, show abnormalities of auditory brain stem response. Cruickshank et al[7] observed a slight prolongation of latencies of brain stem components or loss of some of these components in 4 of 16 patients. Castillo et al[8] observed a unilateral increase of the I-V interpeak latency in 1 of 5 patients.

Sensorineural hearing loss, including one case of mixed hearing loss, was bilateral in all cases in our study. In most of the patients, hearing impairment was severe for their ages and they had no clear cause for hearing impairment. This suggests that the incidence of hearing impairment in HAM is probably higher than that considered previously.[3,5] A reason for the difference between the incidence in our study and that of Kakigi et al[5] may be that the patients we tested were in a clinically more advanced state than the patients in their study. However, the hearing impairment may have been caused by another disease, eg, presbycusis. In order to clarify this point, we intend to perform audiologic studies in these patients after steroid therapy.

Furthermore, the auditory brain stem response for both ears of five patients showed increases of wave I, III, and V peak latencies, with those of the III and V peak latencies being of a marked degree, and increases of the I-III and I-V interpeak latencies. This incidence of abnormalities in auditory brain stem response was also higher than that in patients with HAM and tropical spastic paraparesis in other studies.

In the presence of high-frequency sensorineural hearing loss, wave I peak latency may be prolonged, although wave III and V peak latencies may be slightly affected.[9] Thus, our results suggest possible supranuclear involvement of the auditory system in the brain stem.

Additionally, Arimura et al[4] reported that weak changes in smooth pursuit movement patterns were observed in 50% of their patients, of whom two had transient diplopia and two others had superimposed nystagmus and horizontal eye movement, suggesting that these features might be caused by supranuclear involvement in the oculomotor system. Moreover, Akizuki et al[10] and Iwasaki[11] observed that in HAM

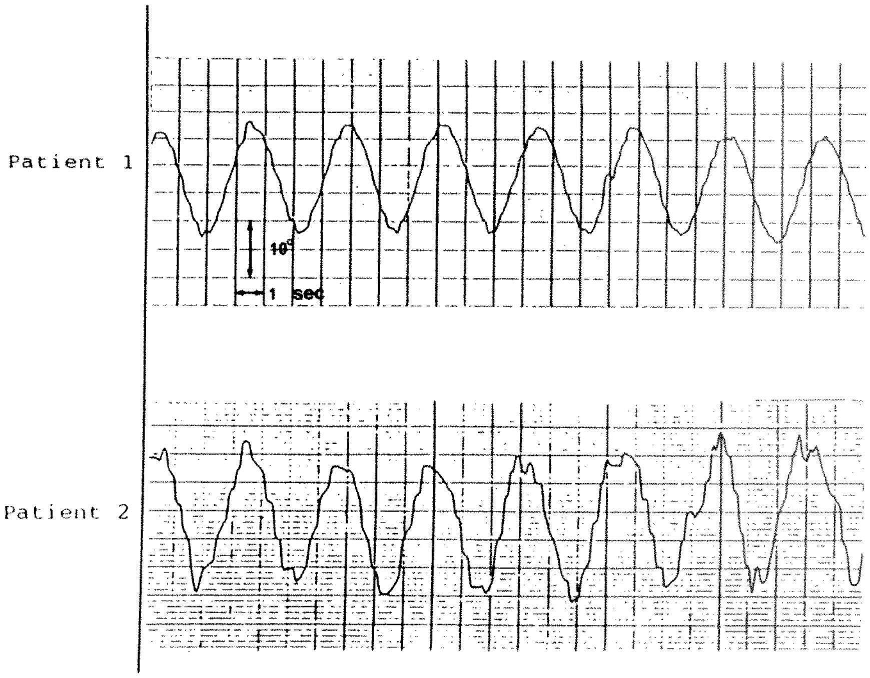

Fig 2. Eye tracking test recordings for two of eight patients. Patients showed superimposed fast saccadic movements of 2/s to 3/s and velocity of over 300°/s to sinusoidal curve. They had no nystagmus and no abnormality on optokinetic pattern test.

cases, perivascular lymphocyte cuffing was also present in the medulla, pons, and white matter of the cerebrum and cerebellum, although marked involvement was found in the spinal cord.

Our patients, in contrast, showed no abnormality on the optokinetic pattern test, and no evidence of cerebellar involvement: no limb ataxia, no dysmetria on the movement of extremities, no truncal ataxia, and no ataxic gait. However, in the smooth pursuit test, the superimposed fast saccadic movements to a sinusoidal curve observed in two patients who had no nystagmus suggested a disturbance of the horizontal oculomotor system in the brain stem, as Arimura et al[4] have observed previously. We also suspect that this abnormality was possibly caused by brain stem involvement in HAM, as recognized previously by Akizuki et al.[10]

In addition, the unilateral canal paresis following caloric stimulation might be caused by involvement of the medulla as part of a series of HAM involvements. However, as far as these abnormalities of the caloric test are concerned, the possibility still remains that vasculitis may induce peripheral vestibular disturbance. In tropical spastic paraparesis cases, Mani et al[6] observed vestibular-type nystagmus in some patients. This finding suggests that the perivasculitis observed in HAM may also involve the peripheral vestibular organs.

Last, since the durations of illness in our patients were varied, ranging from 9 months to 31 years, we investigated whether the abnormalities observed in our study correlated with the duration of illness, but we found no such correlations. This fact may suggest that the neuro-otologic symptoms in HAM patients are caused by not only degeneration, but also other pathogenesis, including vasculitis. In order to clarify this problem, we intend to do a detailed follow-up study of HAM patients.

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INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients being treated with VANCENASE AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use VANCENASE AQ Nasal Spray at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of VANCENASE AQ Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions carefully.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild, transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

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BRIEF SUMMARY

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INDICATIONS AND USAGE VANCENASE POCKETHALER Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

VANCENASE POCKETHALER Nasal Inhaler is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies in seasonal and perennial rhinitis have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Although systemic effects are minimal at recommended doses, VANCENASE treatment should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. VANCENASE treatment should not be used in the presence of untreated, localized infection involving the nasal mucosa.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE POCKETHALER Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients, previously treated for prolonged periods with systemic corticosteroids, are transferred to VANCENASE POCKETHALER Nasal Inhaler. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Extremely rare instances of nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE POCKETHALER Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE POCKETHALER Nasal Inhaler may suppress HPA function.

VANCENASE treatment should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE POCKETHALER Nasal Inhaler to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE Nasal Inhaler should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of the VANCENASE product into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE treatment over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

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Impairment of fertility, as evidenced by inhibition of the estrus cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrus cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

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Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE POCKETHALER Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes. Adverse reactions reported in controlled clinical trials and in long-term open studies in patients treated with VANCENASE Nasal Inhaler are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of VANCENASE Nasal Inhaler have been reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children.

Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely. (See **PRECAUTIONS.**)

Transient episodes of epistaxis or bloody discharge from the nose have been reported in 2 per 100 patients.

Ulceration of the nasal mucosa has been reported rarely.

Extremely rare instances of nasal septum perforation have been reported following the intranasal application of aerosolized corticosteroids. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm have been reported following the oral and intranasal inhalation of beclomethasone.

Increased intraocular pressure has been reported rarely. (See **PRECAUTIONS.**)

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome could occur.

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One canister of VANCENASE POCKETHALER Nasal Inhaler contains 8.4 mg of beclomethasone dipropionate; therefore acute overdosage is unlikely.

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COMPARISON OF HALF-BAND AND FULL-BAND ELECTRODES FOR INTRACOCHLEAR ELECTRICAL STIMULATION

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MELBOURNE, AUSTRALIA

It was hypothesized that intracochlear stimulating electrodes oriented toward the modiolus would require a lower stimulus current to elicit a threshold neural response than longitudinal band electrodes. Electrically evoked auditory brain stem responses (EABRs) and electrode impedances were recorded with full-band and oriented half-band scala tympani electrodes in anesthetized, deafened cats. To elicit a threshold EABR, the stimulus current required for stimulation through half-band electrodes oriented toward the modiolus was not significantly different from the current required for stimulation through full-band electrodes. The impedances of full-band electrodes were significantly lower than those of half-band electrodes. Considering the significantly higher impedance and current density of half-band electrodes in comparison to full-band electrodes, as well as the critical orientation of half-band electrodes during implantation, we believe that full-band electrodes have advantages over half-band electrodes for scala tympani implantation.

KEY WORDS — cochlear implant, electrically evoked auditory brain stem response, half-band electrode.

INTRODUCTION

For the improvement of cochlear prostheses, it is desirable to stimulate discrete groups of auditory nerve fibers with the minimum current. A model of electrical stimulation of the cochlea[1] has predicted the stimulus current required to elicit a threshold neural response to be lower for stimulation through a longitudinal pair of electrodes close to and oriented toward the modiolus than for stimulation through the banded electrode array used by the University of Melbourne/Cochlear[2] device. There are two possible reasons for this to be so. First, the banded array was modeled to lie further from the modiolus, and the distance between the electrode and the modiolus has been shown to be important in determining stimulus current at threshold.[3] Second, the banded array was nondirectional, whereas the longitudinal pair was oriented toward the modiolus. If the electrodes are oriented toward the modiolus, it is possible that the current spread will be directed toward the modiolus, thereby reducing the stimulus current required to evoke a threshold neural response. It was hypothesized that the stimulus current required to evoke a threshold neural response for stimulation through half-band electrodes oriented toward the modiolus would be lower than that for stimulation through full-band electrodes. We tested this hypothesis in the anesthetized, deafened cat by comparing electrically evoked auditory brain stem responses (EABRs) elicited by stimulation through full-band and half-band scala tympani electrodes.

MATERIALS AND METHODS

Electrode Array. The electrode array consisted of three pairs of accurately aligned half-band platinum electrodes on a Silastic MDX-4-4210 carrier (Fig 1). The radius of each electrode was 0.25 mm and the width was 0.3 mm. Each half-band electrode was connected to a platinum-iridium wire. The gap between each pair of half-band electrodes was 0.1 mm, edge to edge, and the distance between the adjacent pairs of electrodes, center to center, was 0.75 mm. The three pairs of half-band electrodes occupied the first 2.2 mm for the tip. At 6 mm from the tip, there was a banded dummy electrode used as a guide to insertion depth during the operation. Between 7 and 9 mm from the tip, a longitudinal Silastic mark was made to assist in the orientation of the electrodes.

Animals. Two adult cats were used in this study. They had otoscopically normal tympanic membranes and normal hearing thresholds (<37dB peak equivalent sound pressure level re 20 $\mu N/mm^2$) as measured by click-evoked auditory brain stem responses (ABRs). Under anesthesia of Saffan (Alphaxalone, 9 mg/kg, intravenously), the animals were profoundly deafened by the coadministration of kanamycin sulfate (300 mg/kg, intramuscularly) and ethacrynic

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From the Department of Otolaryngology, The University of Melbourne, Melbourne, Australia. This study was supported by the grants Studies on Pediatric Auditory Prosthesis Implants from the US National Institutes of Health (contract NO1-DC-7-2342) and Studies to Develop Sensory Prostheses for Deaf Children and Adults from the National Health and Medical Research Council of Australia. The study was conducted in accordance with the Australian National Health and Medical Research Council's guidelines for the care of animals in scientific experiments. The animal use protocol was approved by the Institutional Animal Care and Use Committee of the University of Melbourne.

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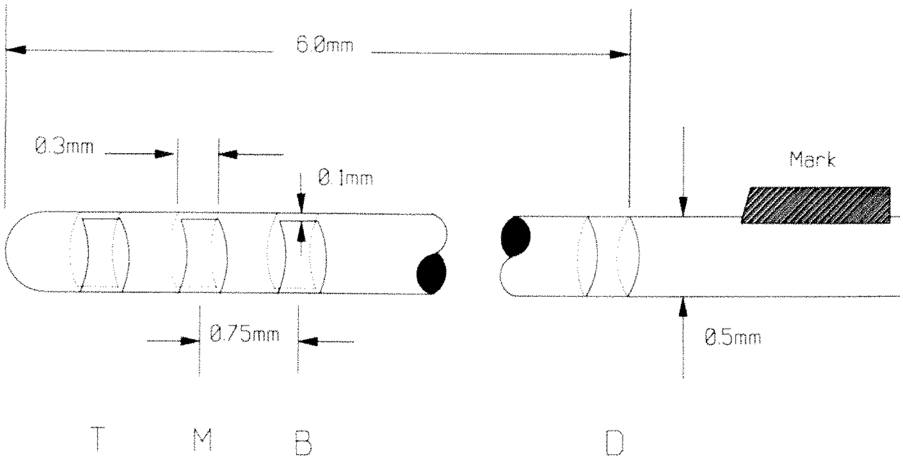

Fig 1. Electrode array consisting of three pairs of half-band electrodes, dummy electrode, and orientation mark on Silastic carrier. T — tip electrodes, M — middle electrodes, B — basal electrodes, D — dummy electrode.

acid (Merck Sharp & Dohme, ethacrynate sodium, 15 to 25 mg/kg, intravenously).[4] Two and a half years later, acute electrical stimulation was conducted on the two cats under general anesthesia (ketamine, 18 mg/kg, intramuscularly, and xylazine, 38 mg/kg, intramuscularly). Anesthesia was maintained by supplemental doses of ketamine (10 mg, intravenously) and xylazine (2 mg, intravenously) as required. Click-evoked ABR thresholds were confirmed to be above 97 dB peak equivalent sound pressure level, the maximum output of the speaker. A postauricular incision was made and the bulla and the round window were exposed. The inferior-posterior edge of the round window niche was trimmed so that after the round window was opened, the modiolus, osseous spiral lamina, and basilar membrane could be clearly brought into view. The electrode array was inserted 6 mm into the scala tympani with three half-band electrodes oriented toward the modiolus and their counterparts oriented toward the outer wall of the scala tympani (Fig 2). After the lead wire was fixed at the bulla wall, the orientation of the electrode array was checked and a small piece of muscle was packed at the round window. Both cochleas in each cat were stimulated, but the results from the right cochlea in one cat were discarded because the stimulus current polarity was not controlled in this cochlea.

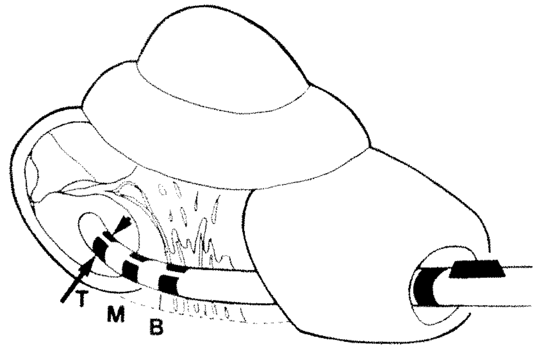

Fig 2. Inner half-band electrodes (arrowhead) oriented toward modiolus and outer half-band electrodes (arrow) oriented toward outer wall of scala tympani. T — tip electrodes, M — middle electrodes, B — basal electrodes.

Impedance Measurement In Vitro and In Vivo. Before the operation, the electrode array was immersed in normal saline. Biphasic pulses of constant current (1.0 mA, 100 microseconds per phase) were delivered to each pair of electrodes, and the electrode voltage and current were shown on an oscilloscope. The voltage across the electrodes is proportional to their impedance. These measurements were repeated after the electrode array was inserted into the scala tympani. Differences in resistance and impedance between half-band and full-band electrodes were tested for statistical significance with a paired comparison *t* test.

EABRs. Electrical stimuli were biphasic, charge-balanced current pulses (200 microseconds per phase, 30 pulses per second). Bipolar stimulation was delivered between two longitudinally placed electrodes (tip-middle, middle-basal, or tip-basal). These electrodes were either half-band or full-band electrodes (Fig 3). The inner half-band electrodes were oriented toward the modiolus, and the outer half-band electrodes were oriented toward the outer wall of the scala. Stimulation through a full-band electrode was achieved by the parallel connection of both inner and outer half-band electrodes.

The EABRs were recorded with subcutaneous needle electrodes (positive at the vertex; negative at the nucha; ground at the abdomen). The gain of the differential preamplifier (WPI, DAM-5A) was 60 dB, and the signals were further amplified by 40 dB. The electrical artifact was suppressed by a sample and hold circuit that released following the electrical stimulus. The signals were filtered by a 50-Hz rejection filter and a band pass filter (Krohn-Hite 3750, high pass 150 Hz, 24 dB per octave; low pass 3 kHz, 6 dB per octave). The EABRs were sampled by an analog to digital converter and averaged over 500 trials. For each current level, two sets of averaged

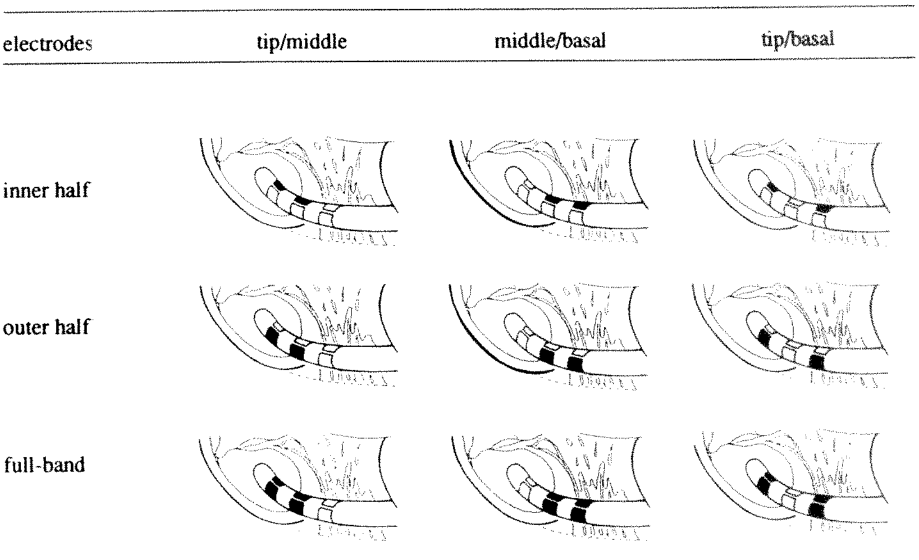

Fig 3. Summary of electrical stimulation paradigms used. Filled electrodes indicate those activated during various modes of electrical stimulation. For electrical stimulation using full-band electrodes, inner and outer half-band electrodes of each pair are connected, having same electrical potential, and current is only between electrodes placed longitudinally.

responses were stored in an IBM-compatible personal computer. The amplitude of the response was measured as the amplitude of the wave P3-N4 (latency between 2.5 and 3.5 milliseconds). The current level at which the EABR amplitude was 0.5 μV was estimated by linear interpolation and arbitrarily defined as threshold. Differences in stimulus current required to evoke a threshold EABR between stimulation through half-band and full-band electrodes were tested for statistical significance with a paired comparison *t* test.

RESULTS

Impedance. On the injection of current through electrodes placed in electrolyte, the voltage across the electrodes increases rapidly to a level proportional to the access resistance of the electrodes (Fig 4). There is also a voltage increase with a longer time constant. The maximum voltage across the electrodes is proportional to the peak impedance of the electrodes, which includes resistive and reactive components. Full-band electrodes had significantly lower access resistances and peak impedances than either of the component half-band electrodes in vivo (see Table) and in vitro (p < .05). There were no significant differences (p > .05) between the in vivo and in vitro measurements of the access resistance or peak impedance.

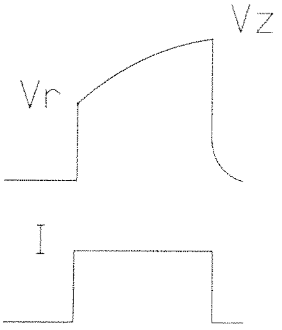

Fig 4. Voltage across electrodes immersed in electrolyte (upper trace) on injection of constant current (I; lower trace) increases rapidly to level (Vr) that is proportional to access resistance of electrodes. Voltage across electrodes increases further to level (Vz) that is proportional to peak impedance of electrodes for pulse duration used.

EABR Amplitude. The amplitude of the EABR increased with increasing current (Fig 5). The P3-N4 wave (wave IV) could be reliably measured over a wide range of currents without interference from electrical stimulation artifact. The amplitude of wave IV of the EABR was measured for different electrode configurations for currents up to 1 mA peak. When data from all electrodes, cochleas, and currents were pooled, the EABR amplitude elicited by stimulation through full-band electrodes was slightly but significantly less than that elicited by stimulation through the inner half-band electrodes (p < .01, paired *t* test). However, this difference was not as large as that between the amplitudes of the EABRs elicited by full-band and outer half-band stimulation (Fig 6). These differences in EABR amplitude were larger for stimulation between longitudinally adjacent elec-

ACCESS RESISTANCE AND PEAK IMPEDANCE OF ELECTRODES IN VIVO

Electrodes	*Tip-Middle*	*Middle-Basal*	*Tip-Basal*
Inner half-band	(1.6) 4.0	(1.6) 3.8	(1.6) 4.0
Outer half-band	(2.0) 4.6	(1.6) 4.2	(1.8) 4.4
Full-band	(1.0) 3.2	(1.0) 3.1	(1.1) 3.3

Data are in kilo-ohms. Access resistances (in parentheses) and peak impedances of electrodes in left cochlea of cat 513 were significantly lower for full-band electrodes than for either of half-band electrodes (p < .05). Activated electrodes are indicated in Fig 3.

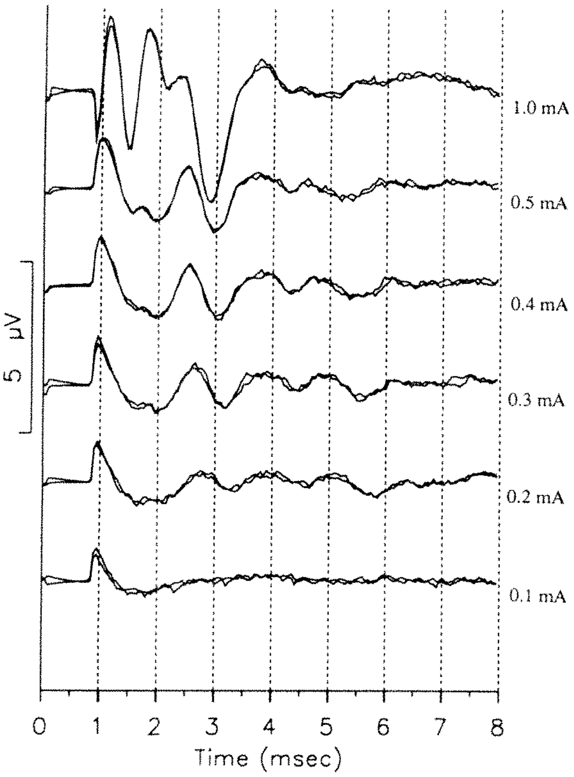

Fig 5. Two averages of electrically evoked auditory brain stem response (EABR) to electrical stimulation were recorded for each current level. Responses illustrated are to stimulation through full-band tip-basal electrodes in right cochlea of cat 513. Amplitude of EABR was obtained by measuring P3-N4 wave (latency of 2.5 to 3.5 milliseconds).

trodes than for stimulation between the tip and basal electrodes.

EABR Threshold. An EABR wave IV amplitude of 0.5 µV was arbitrarily defined as a threshold response. The stimulus current required to elicit a threshold response was estimated by linear interpolation of the EABR input-output functions. It was generally found that stimulation through full-band electrodes required a slightly higher current to evoke a threshold EABR than did stimulation through the inner half-band electrodes, but required much less than did stimulation through the outer half-band electrodes (Fig 7). The current required for a threshold EABR was less for widely spaced electrodes (tip-basal) than for longitudinally adjacent electrodes (tip-middle or middle-basal). Higher stimulus currents were required to elicit a threshold EABR for cochlea 513L than for the other two cochleas. This may have resulted from a difference in the survival of auditory nerve fibers, or a slight difference in the radial position of the electrode within the scala. There was no significant difference ($p > .05$) in the current required to elicit a threshold EABR between stimulation through the inner half-band and full-band electrodes. The stimulus current required to evoke a threshold EABR was significantly higher ($p < .01$) for stimulation through the outer half-band than through either the inner half-band electrodes or the full-band electrodes.

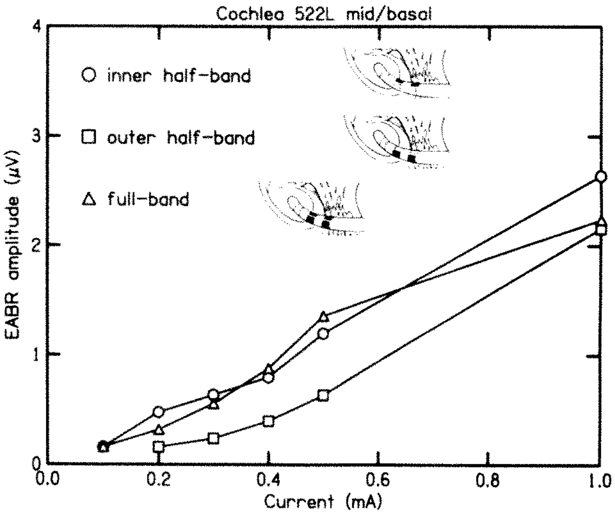

Fig 6. Amplitude of EABR as function of stimulus current for middle and basal electrodes in cochlea 522L. Stimulation was delivered through inner half-band, outer half-band, and full-band electrodes. Stimulation through inner half-band electrodes generally evoked similar or slightly larger EABR amplitude than did stimulation through full-band electrodes, and much larger amplitude than did stimulation through outer half-band electrodes.

DISCUSSION

This study investigated differences in EABR amplitude, stimulus current at EABR threshold, and electrode impedance between stimulation through half-band and full-band scala tympani electrodes. Stimulation through full-band electrodes evoked a threshold EABR at current levels not significantly different from those evoked by stimulation through half-band electrodes oriented toward the modiolus. The access resistance and peak impedance of full-band electrodes were significantly lower than those

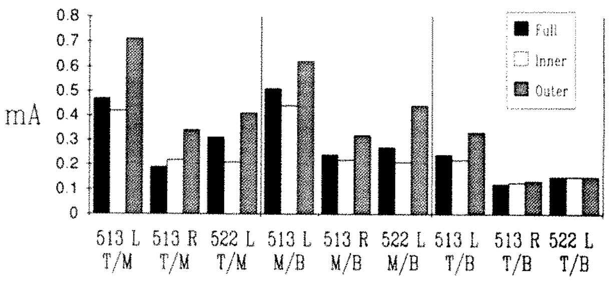

Fig 7. Stimulus current required to elicit threshold EABR for stimulation through full-band, inner half-band, and outer half-band electrodes. Activated electrodes are indicated in Fig 3. T/M — tip-middle electrodes; M/B — middle-basal electrodes; T/B — tip-basal electrodes; L — left ear; R — right ear; 513, 522 — cat numbers.

of half-band electrodes.

A previous study of half-band electrodes was conducted,[5] but the EABR was contaminated by electrophonic components.[6] In order to study direct electrical stimulation of the auditory nerve without contamination of the EABR by electrophonic responses, we deafened the cats with kanamycin and ethacrynic acid.[4] This technique results in a loss of spontaneous and acoustically evoked activity in auditory nerve fibers (R. K. Shepherd and E. Javel, unpublished observations, 1987), as well as a complete bilateral loss of hair cells and a moderate to severe loss of spiral ganglion cells.[7] These animals should therefore be good models of profoundly deaf patients.

The EABR had a slightly larger amplitude and a threshold response was elicited by slightly lower stimulus currents when stimulation was delivered through the inner half-band electrodes, rather than through the full-band electrodes. However, the difference in stimulus current required to evoke a threshold response was not statistically significant. The EABR had a significantly lower amplitude and a significantly higher current was required to elicit a threshold response when stimulation was delivered through the outer half-band electrodes than when it was delivered through either the inner half-band or full-band electrodes. The clinical implication of these results is that patients may not gain significant improvement by using inner half-band electrodes instead of the full-band electrodes. Furthermore, a large fenestration at the cochlea is needed for accurate orientation of the half-band electrode, and if the electrode array is rotated during or after insertion, the current required to evoke a threshold neural response may be significantly higher than for the full-band electrode.

The access resistances and peak impedances of full-band electrodes were significantly lower than those of half-band electrodes. This would result in a greater range of currents being available to the full-band electrodes without exceeding the maximum voltage output of the stimulator. The lower impedance of the full-band electrodes indicates the passage of electrical current through the whole surface of the full-band electrodes, resulting in a lower charge density than that for the half-band electrode. For the full-band electrode, stimulation at 1 mA for 100 microseconds per phase results in a charge density of 21.2 microcoulombs per square centimeter per phase. Stimulation through the half-band electrodes would result in a charge density of 42.4 microcoulombs per square centimeter per phase, which is close to the levels that cause cochlear damage.[8] From considerations of surgical implantation, impedance, and charge density, we conclude the full-band electrodes to be more suitable for cochlear implantation than half-band electrodes.

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IMMUNOHISTOCHEMICAL LOCALIZATION OF A CYTOCHROME P-450 ISOZYME IN HUMAN NASAL MUCOSA: AGE-RELATED TRENDS

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Immunoperoxidase staining with an antibody to cytochrome P-450 (NMa) was used to investigate the localization of this isozyme in the human nasal mucosa. Olfactory mucosa was identified by staining of olfactory receptor cells with an antibody to olfactory marker protein. Immunoreactivity to NMa was localized in sustentacular cells in the olfactory epithelium, and in Bowman's gland acinar cells and vascular endothelial cells in the lamina propria. In the respiratory mucosa, ciliated epithelial cells, as well as serous gland acinar cells and vascular endothelial cells in the lamina propria, were immunoreactive for this isozyme. An age-related decrement in the intensity and extent of immunoreactivity within these cells was noted in nasal tissue from patients 60 years of age and over when compared with that of patients under 60 years of age. These results identify sites of xenobiotic metabolism or activation in human nasal mucosa.

KEY WORDS — Alzheimer's disease, cytochromes P-450, nasal mucosa, olfactory mucosa.

INTRODUCTION

The cytochrome P-450 isozymes are key biotransformation enzymes that metabolize endogenous as well as xenobiotic compounds. The general reaction catalyzed by a cytochrome P-450 monooxygenase is the addition of one oxygen atom to a lipophilic organic substrate, rendering it polar and thus more water-soluble (a phase I reaction). The modified organic molecule may then become a substrate for phase II reactions, in which it is conjugated to an endogenous substrate that targets it for clearance from the tissue. The nasal mucosa has the highest concentrations of cytochromes P-450 among extrahepatic tissues in nonprimate mammals.[1] In cynomolgus monkeys, all measurable nasal cytochrome P-450 activity is present in the olfactory mucosa.[2]

Each tissue active in biotransformation appears to have a spectrum of isozymes of cytochromes P-450, some of which may be tissue-specific; for example, rabbit nasal mucosa has different P-450 isozymes with distinct enzymatic properties compared to tissue from other regions of the respiratory tract.[3] The isozymes in various tissues may differ in concentration, catalytic activity, substrate specificity, and/or susceptibility to regulatory factors such as chemical inducers. For example, nasal cytochromes P-450 have different substrate specificities than those in the liver: the nasal procarcinogen hexamethylphosphoramide is a better substrate for canine nasal cytochromes P-450 than benzo[*a*]pyrene, which is a better substrate for the liver enzymes.[2] In addition, the levels of cytochromes P-450 in each individual may vary, depending on his or her genetics, nutritional and hormonal status, alcohol and tobacco use, and exposure to environmental xenobiotics, some of which may induce or repress expression of the genes encoding the cytochrome P-450 enzymes.[4]

Among the potential substrates of cytochromes P-450 in the nasal cavity are odorous organic hydrocarbons and other natural products, therapeutic drugs, volatile carcinogens found in herbicides and other environmental xenobiotics, exogenous and endogenous steroids, and arachidonic acid. Studies utilizing antibodies generated to various isoforms of cytochromes P-450 have demonstrated localization of several cytochrome P-450 enzymes in superficial

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TABLE 1. SOURCES OF HUMAN NASAL MUCOSA

Pt	Age (y)	Sex	Cause of Death	PMI (h)	FT (h)
1	24	M	Gunshot wound (chest)	22	3
2	39	M	Coronary artery disease	12	2
3	47	F	Gunshot wound (chest)	17	1
4	50	F	Liver disease	5	4
5	52	M	Coronary artery disease	7	2
6*	52	M	Bronchopneumonia, sepsis	4	4
7	63	M	Aortic aneurysm	13	3
8	69	F	Pulmonary embolism	16	1
9	72	M	Pancreatic cancer	3	3
10*	72	F	Upper gastrointestinal tract hemorrhage	3	5
11*	72	M	Emphysema	4	5
12	76	M	Metastatic cancer	4	1
13*	77	M	Respiratory failure	3	2
14	80	F	Cerebral edema	10	2
15*	85	F	Possible closed head injury	2	2
16	90	M	Hypertension	20	2

PMI — postmortem interval, FT — fixation time.

*Preliminary diagnosis of Alzheimer's disease confirmed in each case by examination of brain sections for presence of characteristic numbers and locations of senile plaques and neurofibrillary tangles.

epithelial cells and glands in the nasal mucosa of rodents.[5-7] Microsomes prepared from human nasal respiratory mucosa exhibit high levels of activity toward diethylnitrosamine, a P-450 substrate present in tobacco smoke[8]; direct measurements show that human respiratory microsomal preparations have about 5% of the cytochrome P-450 activity measured in human hepatic microsomes.[9] Although more than 30 P-450 enzymes have been identified in humans,[10] the localization of cytochrome P-450 isozymes in human nasal mucosa has not been previously reported. The purpose of this study was to investigate the cellular localization of cytochromes P-450 in human olfactory and respiratory mucosae in order to identify sites of xenobiotic metabolism in the human nasal mucosa.

MATERIALS AND METHODS

Human nasal mucosa was obtained at autopsy from 16 patients (Table 1) through either the Kentucky Medical Examiner Program or the Alzheimer's Disease Research Center of the Sanders-Brown Center on Aging. After removal of the brain, the cribriform plate was isolated with an electric saw, lifted out along with the upper part of the nasal septum, and placed immediately in ice-cold Zamboni's fixative (2% paraformaldehyde and 0.15% picric acid in 0.1 mol/L phosphate buffer, pH 7.35) for 1 to 5 hours. The mucosa was carefully dissected from the bone and cartilage, incubated sequentially in 10%, 20%, and 30% sucrose in phosphate-buffered saline, embedded in OCT compound, frozen on dry ice–alcohol, and sectioned at 15 μm. Sections were collected on chrom-alum-gelatin–coated slides and stored at −20°C until stained.

Polyclonal antibodies were generated against two cytochrome P-450 isoforms, designated NMa and NMb, that were isolated and purified from nasal microsomes derived from primarily olfactory mucosa in the rabbit nasal cavity.[11,12] Biochemical and immunochemical studies have demonstrated that NMa is present in both olfactory and respiratory mucosae, and NMb is present in olfactory mucosa. Antibody to NMa was prepared in rabbits and recognizes an antigen present in nasal mucosa and liver, but not lung. Antibody to NMb was prepared in sheep; the immunoglobulin G fraction was made monospecific by adsorption on a column containing proteins from the 7% to 14% polyethylene glycol fraction of solubilized rabbit hepatic cytochromes, and recognizes an antigen present only in olfactory tissue.

Immunohistochemistry was performed using standard avidin-biotin staining techniques with the appropriate species-specific Vectastain kits (Vector Laboratories, Burlingame, Calif) and 3-amino-9-ethylcarbazole (Polysciences, Inc, Warrington, Pa; Chromored) as the chromogen. Endogenous peroxidase was quenched with 5% hydrogen peroxide in 50% methanol for 30 minutes. To identify olfactory epithelium unequivocally, representative sections from each tissue block were stained with the antibody to olfactory marker protein (1:2,000), generously supplied by Dr Frank Margolis (Roche Institute of Molecular Biology, Nutley, NJ). The presence of olfactory marker protein–positive neurons in the epithelial layer characterized olfactory epithelium. Optimal dilutions of α-NMa for staining human nasal mucosa were 1:850 to 1:1,500; α-NMb did not cross-react specifically with human tissue at the nine dilutions (1:50 to 1:3,500) tested.

Staining specificity was assessed by omitting the primary antibody from the staining protocol, and by preabsorbing α-NMa (1:1,000 dilution) with 1:50 or 1:100 dilutions of a preparation of cytochromes P-450 from rabbit hepatic microsomes. Sections of rat liver stained at the same time as the human tissue were used as a positive control.

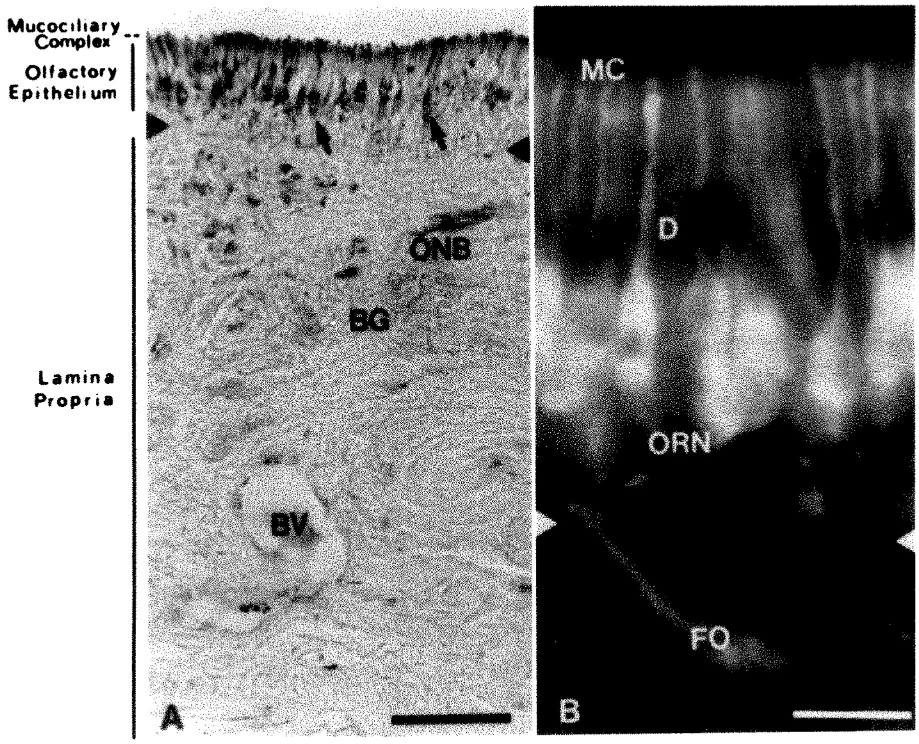

Fig 1. Organization of human olfactory mucosa. A) (Patient 7) Immunoperoxidase staining with antibody to olfactory marker protein (OMP) demonstrates presence of olfactory receptor cells within neuroepithelium (arrows). Lamina propria contains bundles of OMP-positive olfactory nerves (ONB), Bowman's glands (BG), and blood vessels (BV) in connective tissue stroma. Triangles — approximate position of basement membrane, bar — 50 µm. B) (Patient 3) Immunofluorescence staining of olfactory receptor cells in olfactory mucosa with antibody to OMP demonstrates thin dendrites (D) whose apical cilia terminate in mucociliary complex (MC) at neuroepithelial surface, cell bodies that contain nucleus (ORN), and axons that penetrate basement membrane (white triangles) in thin bundles (fila olfactoria; FO). Wide dark spaces between receptor cells are occupied by sustentacular cells. Bar — 20 µm.

RESULTS

Identification and Organization of Human Olfactory Mucosa. The cellular organization of the human olfactory mucosa, with olfactory marker protein–immunoreactive receptor cells in the epithelium, is shown in Fig 1A. The epithelium contains 1) olfactory receptor cells (Fig 1B), whose dendrites terminate in cilia that lie in a surface mucus layer, and whose axons pass through the basement membrane, and together with axons from other receptor cells, form the olfactory nerve, which terminates in the olfactory bulb; 2) sustentacular cells, whose broad apical surfaces, bearing microvilli, lie between receptor cell dendrites, and whose foot processes extend to the basement membrane; and 3) basal cells, which lie along the basement membrane, and some of which are progenitors of the olfactory receptor cells. The lamina propria contains Bowman's glands (serous glands unique to the olfactory mucosa); olfactory, autonomic, and trigeminal nerves; blood vessels; and connective tissue.

NMa Localization in Olfactory Mucosa. NMa immunoreactivity was localized in sustentacular cells in the olfactory epithelium (Fig 2A,B) and in acinar cells of Bowman's glands (Fig 2C) and endothelial cells of blood vessels (not shown) in the lamina propria. Sustentacular cell immunoreactivity generally was uniformly distributed throughout the cell, from the supranuclear region at the mucosal surface to the foot process at the basement membrane. In Bowman's glands, diffuse immunoreactivity throughout the acinar cell, with the exception of the nucleus, was observed. The presence of lipofuscin granules in the supranuclear region of the acinar cells made it difficult to determine unequivocally if immunoreactivity was associated with secretory granules. However, the apparent absence of immunoreactivity in the surface mucus (Fig 2B) reinforces the impression that the immunoreactivity was diffuse rather than granular. Intraepithelial duct cells of Bowman's glands were not immunoreactive. Occasionally, clusters of sustentacular and acinar cells that stained more intensely than surrounding immunopositive cells were observed. Endothelial cells of arterioles, venules, and the vasa nervorum in olfactory nerve bundles also displayed immunoreactivity for NMa.

NMa Localization in Respiratory Mucosa. Immunoreactivity was observed in the brush border of the ciliated columnar epithelial cells, with a less intense reaction in the cell cytoplasm (Fig 3A). Within the brush border, immunoreactivity appeared to be associated with the cilia rather than the mucus. In addition, immunoreactivity was observed throughout serous gland acinar cells, with the exception of the nucleus (Fig 3B). No immunoreactivity was observed in mucous glands (not shown). Immunoreactivity was also observed in endothelial cells (Fig 3B) of most blood vessels.

Age-Related Trends. There were clear trends in the intensity of NMa immunoreactivity and in the distri-

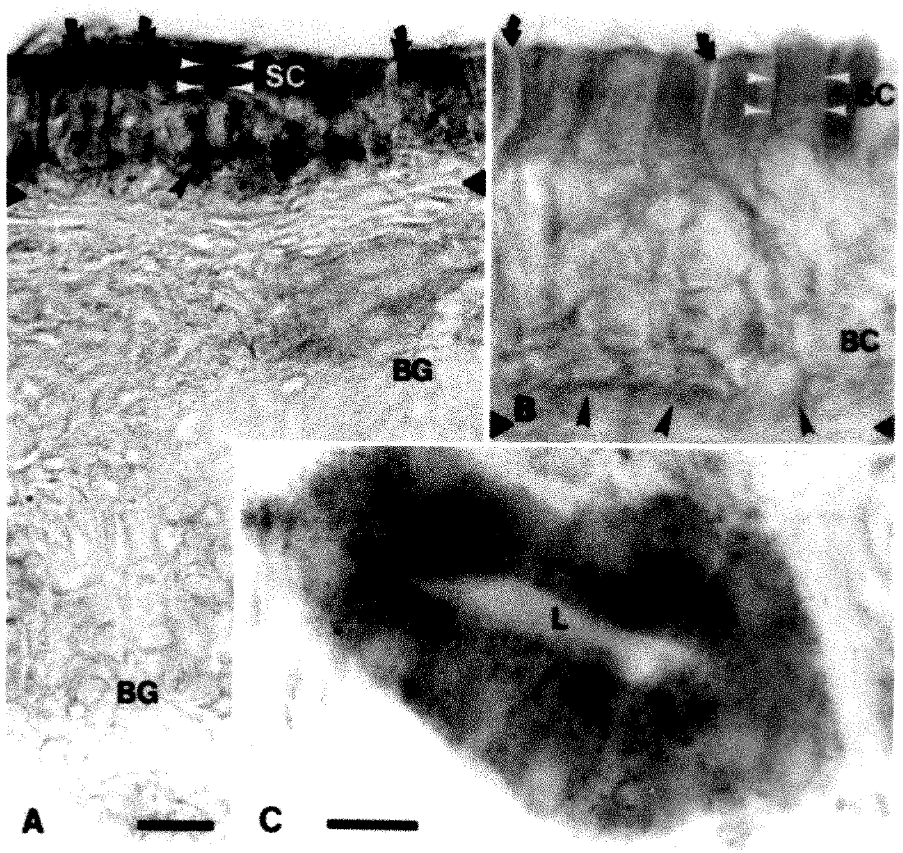

Fig 2. NMa immunoreactivity in olfactory mucosa. A) (Patient 4) Olfactory mucosa of 50-year-old woman exhibits intense staining in supranuclear regions (white arrowheads) and foot processes (black arrowhead) of sustentacular cells (SC). Curved arrows indicate unstained olfactory receptor cell dendrites. Bowman's glands (BG) in lamina propria are less intensely stained. Triangles — position of basement membrane, bar — 20 μm. B) (Patient 10) In olfactory epithelium of 72-year-old woman, immunoreactivity, although less intense, is still evident in supranuclear region (white arrowheads) and foot process region (black arrowheads) of sustentacular cells (SC). Olfactory receptor dendrites (curved arrows) and basal cells (BC) are unstained. Triangles — approximate position of basement membrane. C) (Patient 4) Diffuse cytoplasmic immunoreactivity in Bowman's gland from same patient as in A appears granular because of presence of yellow lipofuscin granules. L — lumen of gland, bar (for B and C) — 10 μm.

bution of cellular staining in the nasal mucosae from different patients (Fig 4). In general, immunoreactivity was most intense in the tissue from young and middle-aged patients (under 60 years old) and was noticeably less intense in tissue from the older patients (60 years old and over). In addition, in tissue from the younger patients, immunoreactivity in olfactory sustentacular cells extended from the supranuclear region to the foot process (Fig 4A), and in respiratory ciliated columnar epithelial cells, from the brush border to the base of the cell. In tissue from older patients, immunoreactivity was restricted to the supranuclear region of the olfactory sustentacular cells (Fig 4B,C) and the brush border of respiratory ciliated columnar epithelial cells. In several of the older patients, there was a more obvious decrease in immunoreactivity in respiratory epithelial cells than in olfactory sustentacular cells. In addition, endothelial cells in older patients displayed no immunoreactivity in sections in which olfactory and respiratory epithelial cells retained weak immunoreactivity. Regional differences in staining intensity were observed within some sections as noted above and between different blocks from the same patient, and in older patients, there was an occasional small cluster of epithelial cells that were stained more intensely than in surrounding regions. In general, however, there was still a clear difference between staining intensity between patients under 60 years of age and those 60 years of age and over. Sections that were evaluated for these comparisons were matched for thickness, antibody concentration (1:1,000), and staining protocol. Only sections stained at the same time were compared with each other. No obvious qualitative differences in NMa localization or staining intensity were observed in the nasal mucosa from patients who had Alzheimer's disease compared to other older patients.

Controls. Omission of the primary antibody from the staining protocol resulted in no specific staining in the tissue, including the endothelial cells, a common site for nonspecific staining by secondary-antibody immunoglobulin G. Preabsorption of the primary antibody with 1:50 and 1:100 dilutions of hepatic microsomal cytochromes P-450 reduced or eliminated immunoreactivity in all sites in a concentration-dependent manner. In sections of rat liver stained with α-NMa, most hepatocytes displayed weak diffuse cytoplasmic immunoreactivity. Strongly immunoreactive hepatocytes tended to occur in clusters around blood vessels. No immunoreactivity was observed in the endothelial cells of the liver.

DISCUSSION

This study demonstrates for the first time the

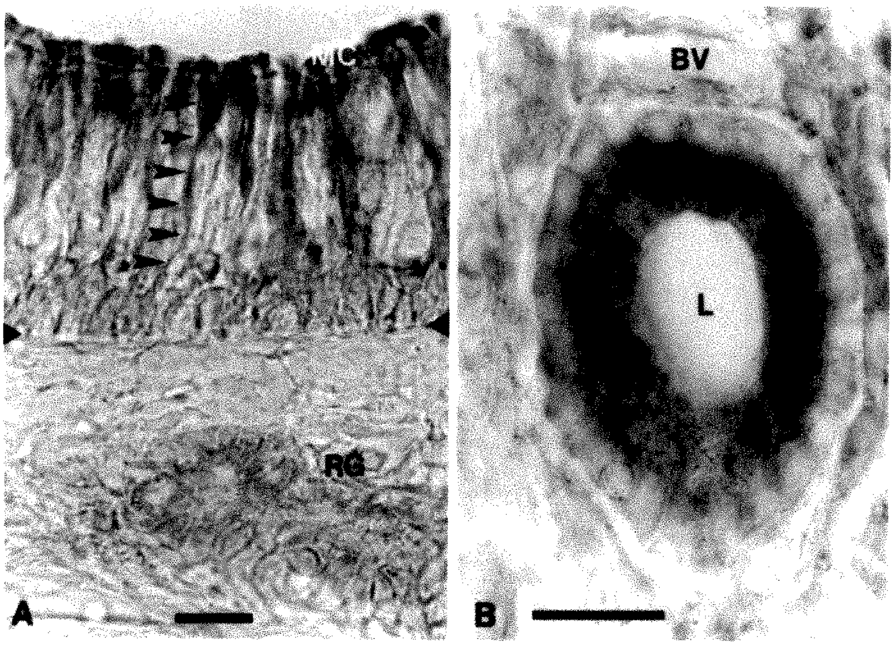

Fig 3. (Patient 3) NMa immunoreactivity in respiratory mucosa. Bars — 20 μm. A) Ciliated cells (arrowheads) in respiratory mucosa of 47-year-old woman are intensely immunoreactive, particularly in brush border region of mucociliary complex (MC). Serous respiratory glands (RG) show less intense immunoreactivity. Triangles — position of basement membrane. B) Cytoplasmic immunoreactivity in serous RG from same patient appears granular because of presence of lipofuscin granules, which are less numerous than in Bowman's glands. Endothelium of blood vessel (BV) is also immunoreactive. L — lumen of gland.

localization of an isoform of cytochrome P-450 in human nasal mucosa. Two important functions for cytochromes P-450 in nasal mucosa have been suggested: to protect the lungs from damage by inactivating inhaled environmental toxicants[2] and to maintain olfactory sensitivity and acuity by facilitating the inactivation and clearance of certain odorants from the vicinity of olfactory receptors.[13-15] However, both of these proposed functions are associated with additional complexities. For example, cytochrome P-450 metabolism often results in bioactivation of xenobiotics to carcinogens rather than detoxification[16,17]; NMa exhibits high catalytic activity toward the procarcinogens hexamethylphosphoramide and *N*-nitrosodiethylamine,[11] as well as nicotine.[18] With respect to olfactory function, cytochrome P-450 metabolism may change a nonodorous substrate into an odorous one, or may alter the odor of an odorous molecule through chemical changes in its structure.[1] Both ethanol and butanol are NMa substrates,[11] and the metabolism of many odorants and procarcinogens by cytochromes P-450 results in the production of the odorant and carcinogen formaldehyde.[19] These considerations suggest that defining the roles of the cytochromes P-450 superfamily in nasal mucosa will depend on the particular substrates being considered. The complexity of functions will increase with the number of active isoforms identified in this tissue, and with their susceptibility to regulatory factors.

The localization of cytochrome P-450 in sustentacular cells and Bowman's glands in the olfactory mucosa of humans is consistent with that observed in the rat olfactory mucosa with α-NMa and α-NMb,[20] as well as other antibodies.[5-7] Bowman's glands and sustentacular cells in the olfactory mucosa of rodents have been previously implicated in the biotransformation of drugs and environmental toxins that are likely cytochrome P-450 substrates,[17,21] and human Bowman's glands have been associated with immune

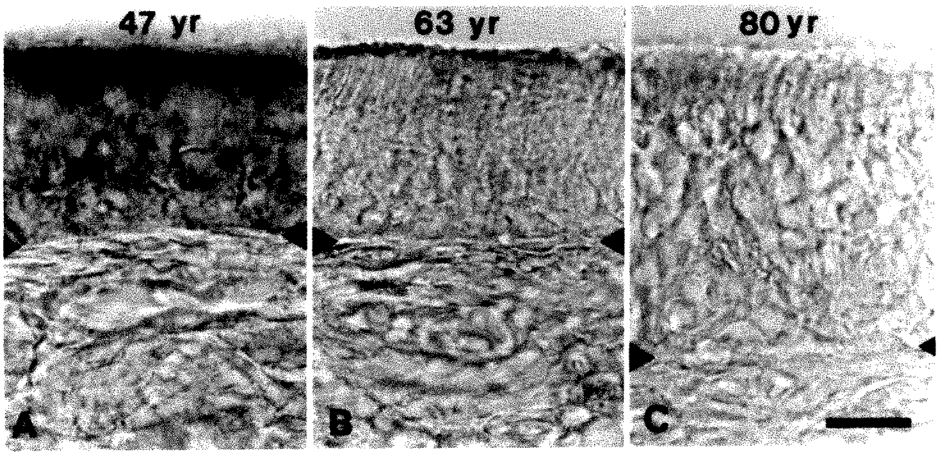

Fig 4. (Patients 3, 7, and 14) Age-related decrease in NMa immunoreactivity in olfactory mucosa. Age of patient from whom tissue was obtained is indicated above epithelium. Clear decrement in intensity and extent of immunoreactivity in sustentacular cells is associated with increasing age. Triangles — position of basement membrane, bar (for A-C) — 20 μm.

TABLE 2. POSTMORTEM INTERVAL AND FIXATION TIME IN PATIENTS UNDER VERSUS OVER 60 YEARS OF AGE

Age (y)	No. Pts	Postmortem Interval (h)			Fixation Time (h)		
		Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
<60	6	11.2	7.2	4-22	2.7	1.2	1-4
≥60	10	7.8	6.5	2-20	2.6	1.4	1-5

defense function.[22,23] Although the functions of human sustentacular cells have not been unequivocally determined, these results suggest that sustentacular cells may interact with constituents of the nasal mucus, in which molecules gaining access to the nasal cavity must dissolve to reach cellular surfaces. Odorants or xenobiotics may enter sustentacular cells by adsorptive endocytosis, in which binding to the cell surface occurs prior to internalization, or by fluid-phase endocytosis, in which fluid and its dissolved contents near the cell surface are internalized. Both smooth endoplasmic reticulum — the subcellular membrane system in which cytochromes P-450 are localized[24] — and vesicles suggestive of the interchange of material with the mucus layer or subepithelial blood vessels have been described in the apices and foot processes of human sustentacular cells.[25,26]

The endothelial localization of cytochrome P-450 isozymes has not previously been described in nasal tissue, although their localization in the endothelium of blood vessels of the lung has been reported in animal models[27] and in humans.[28] Possible functions of the endothelial NMa include the metabolism of substrates from the nasal cavity that gain access to the subepithelial nasal vasculature through paracellular pathways or that exceed the capacity of the nasal enzymes, and metabolism of substrates entering the nasal mucosa through the vascular system. A role for endothelial cytochromes P-450 in vasomotor regulation has been suggested by the observation that arachidonic acid metabolites generated by cytochrome P-450 oxidation are responsible for the endothelium-dependent relaxation observed in rabbit blood vessels.[29]

The age-related decreases in the intensity and distribution of immunoreactivity for NMa are generally consistent with previous observations on xenobiotic-metabolizing forms of P-450 in animal models.[30] However, human hepatic cytochrome P-450IIE1 activity does not decline with age,[31] and a recent review of hepatic drug metabolism in humans[32] concludes that a decrease in hepatic drug-metabolizing enzymes in the elderly has not been established. The results from this study suggest that at least one extrahepatic isoform of cytochrome P-450 may decline in relative concentration with advancing age, with the changes being most prominent after the age of 60 years. This decline does not appear to be correlated with variations in postmortem intervals or fixation times (Table 2). However, these observations are cautiously being described as trends for three reasons: 1) the limited sample size, 2) the subjective nature of the data analysis, and 3) the fact that medical histories were not available for the majority of the patients from whom nasal tissue was obtained, so that potential induction from factors such as smoking, prescribed medications, and occupational exposure to xenobiotics could not be evaluated. It should be noted that the ability of normal, healthy individuals to identify odorants begins a precipitous decline between the ages of 60 and 69 years,[33] although no causal relationship is implied with the results of this study.

The results of our study demonstrate that three sites in human nasal mucosa contain a cytochrome P-450 isozyme that is active in the metabolism of xenobiotics: surface epithelial cells, gland cells, and endothelial cells. These sites are localized to provide the nasal mucosa with protection from xenobiotics arriving at the tissue by inhalation into nasal cavity or by transport via the blood vascular system, or to serve as targets for carcinogens that are activated by P-450 metabolism in these cells.

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BILATERAL PAROTID DUCT FISTULA

CASE REPORT

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Parotid duct fistulas (PDFs) are rare and have various causes such as gunshot wounds and human and animal bites; they may also be congenital. We have not found previous publications on bilateral PDF. Our patient, although young, also had generalized pigmentation characteristic of aging and thick, dry, wrinkled skin, as well as pyoderma. Biochemical analysis was performed on discharge from the patient's face, and histopathologic and immunologic studies were done. The fistulas were treated by intraoral fistulization. Cephalosporins were given to the patient for 5 days postoperatively to treat the pyoderma.

KEY WORDS — **bilateral parotid duct fistula, external parotid duct fistula.**

INTRODUCTION

The parotid duct (Stensen's duct) issues from the anterior border of the parotid gland, passes anteriorly across the masseter muscle, and curves abruptly medially around the anterior border of this muscle. If the duct leaves the cranial portion of the gland, it courses obliquely caudalward about 1.5 cm inferior to the zygoma. If it arises from the central and caudal portion, it passes toward the cranial side in an oblique direction. The duct is accompanied by the transverse facial artery cranially and the infraorbital branch of the facial nerve caudally. It penetrates the fat of the cheek and the fibers of the buccinator muscle, and runs for a short distance between the muscle and the mucous membrane before it terminates in a minute orifice, sometimes on the summit of a little papilla. This opening is opposite the crown of the second superior molar tooth.

Outer fistulas of the parotid duct can be caused by various traumas such as gunshot wounds and bites. The fistula may be congenital.[1] The current surgical treatment is to make a communication by a thin catheter and a suture between the proximal and distal sides of the duct and then leave the catheter in place for 14 days.[2]

CASE REPORT

Our patient, a 12-year-old boy, had changes characteristic of aging on the skin of his face. Since age 2, he had had pigmentation, thickness, dryness, wrinkles, and pyoderma. As a complication of the pyoderma a right Stensen's duct fistula occurred at 4 years of age. Two years later a left Stensen's duct fistula occurred. At age 12 he was admitted to the hospital because of discharge from his face. The parotid duct area showed bilateral parotid fistulas (see Figure). The parotid canal, which is about 3 to 4 mm deep, was detected by a catheter through the orifice in the mouth. There were scars on his eyelids and the rest of his face. In addition, the patient had pigmentation, infected wounds, and scars on the dorsal surfaces of his arms and legs. On biopsy the lesions were seen to be inflammatory in origin, but not pemphigoid. The blood and urine analysis results were normal. Immunologic studies yielded normal results. *Staphylococcus aureus* was found at bacteriologic examination. Histopathologic studies of the skin lesions showed findings of pyoderma. Results of the biochemical analysis of discharge on the patient's face are displayed in the Table. The discharge fluid was saliva from the parotid gland.

Both fistulas were operated on by the same method under general anesthesia. The orifices of the fistulas were similarly at the anterior border of the masseter muscles; on the other hand, this region is also the angle of the parotid duct. Because much of the skin and subcutaneous tissues turned out to be massive scar tissue, an end-to-end anastomosis could not be performed. After the proximal duct was painted with gentian violet, around the orifice of the fistula a

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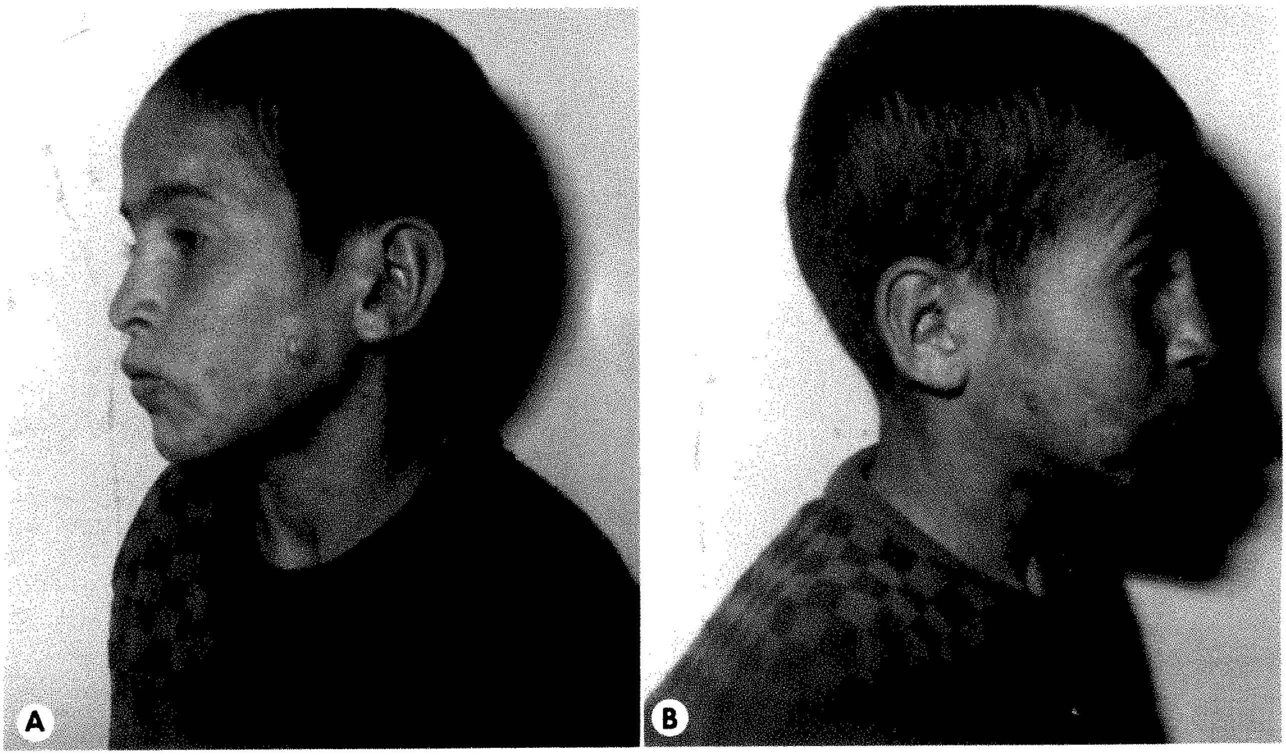

Parotid duct fistulas. A) Left. B) Right.

horizontal ovoid incision was performed and the channel was dissected about 1 cm. The muscle and oral mucosa were perforated. The mucosa was pulled out and sutured to the skin around Stensen's orifice. The skin defect was sutured primarily. For 5 days cephalosporin treatment was given to the patient. Other infectious skin lesions were treated with this therapy. The patient was observed 1 year with no recurrences of pyoderma.

DISCUSSION

Kaufman[3] defined the canalization technique for the treatment for Stensen's duct fistula about 100 years ago. Nicoladoni[4] made the outer fistula an inner fistula by means of mucosal orification. Leriche[5] proposed the decrease of saliva release with incision of the auriculotemporal nerve. Morestin[6] ligated the proximal end of the channel in order to cause atrophy of the gland. Nicoladoni[4] and Payr[7] were the first authors to make an end-to-end anastomosis.

Kitamura and Togawa[8] defined two distinct methods: intraoral fistulization and extraoral ductal surgery. Gilbert[1] reported two congenital Stensen's channel fistula cases associated with branchial arch defects. Bailey[9] has reported the occurrence of a parotid channel fistula in an abcess pouch after removal of mandibular teeth. A biochemical analysis of the saliva was presented by Von Becker et al.[10] Our biochemical findings supported those of Von Becker et al.

Our case is not identical to those of previous studies because of skin infection. Because of the absence of a distal end, an end-to-end anastomosis could not be performed. Instead, cutaneous fistulas were treated by intraoral fistulization. The parotid channel fistulas were caused by skin infection, and it is interesting that the fistulas were bilateral.

Evidence suggested that the skin lesions were due to an unidentified disease involving a congenital defect of the skin's immunity that predisposed it to pyoderma. Rayfield and Challacombe[11] wrote in

RESULTS OF BIOCHEMICAL ANALYSIS OF DISCHARGE FROM PATIENT'S FACE

Parameters	*Results for Patient*	*Normal for Parotid Gland*	*Normal for Sub-mandibular Gland*
Potassium (mEq/dL)	18	20	17
Sodium (mEq/dL)	22	23	21
Chloride (mEq/dL)	21	23	20
Bicarbonate (mEq/dL)	19	20	18
Calcium (mg/dL)	1.8	2	3.6
Magnesium (mg/dL)	0.24	0.2	0.3
Phosphate (mEq/dL)	5.7	6	4.6
Urea (mg%)	13	15	7
Uric acid (mg%)	2.7	3	2
Protein (mg%)	235	250	150
pH	6.7	6.8	7.2

1987, "Although these surfaces are by no means impervious, the severe infections found in patients suffering from burns show just how important this primary mechanical barrier is." The pigmentations, thickness, dryness, and wrinkles could not be ascribed to the presence of pyoderma. They could be considered as symptoms of this unidentified disease. We consider the pyoderma to be a complication of this disease, and the Stensen's duct fistulas to be complications of the pyoderma.

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EFFECTS OF STELLATE GANGLION STIMULATION ON BILATERAL COCHLEAR BLOOD FLOW

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The effect of intraneural electrical stimulation of the stellate ganglion (SG) on bilateral cochlear blood flow (CBF) was investigated with laser-Doppler flowmetry. The SG of 15 anesthetized guinea pigs was exposed by a novel surgical approach and stimulated with a specially designed intraneural bipolar platinum-iridium electrode. Bilateral CBF was continuously monitored. Stimulation of 0.25 mA caused a detectable increase of the systemic blood pressure (BP) and a bilateral decrease of the cochlear vascular conductance (R, defined as the ratio CBF/BP). A stimulus of 0.5 mA elicited a statistically significant ipsilateral CBF (CBFi) decrease of 3.6% ± 5.1% from the baseline and a contralateral CBF (CBFc) decrease of 3.1% ± 5.5%. That no statistical difference was found between CBFi and CBFc indicates that a unilateral sympathetic stimulation of the SG can cause equal bilateral responses. These responses were accompanied by a significantly increased BP (8.7% ± 5.2% of baseline) and consequently a greatly decreased R (12.2% ± 6.5%) of the ipsilateral cochlea. Bilateral sections of the cervical sympathetic trunk below the level of the superior cervical ganglion did not alter the evoked changes in CBF, BP, and R. It is concluded that SG stimulation can decrease the conductivity of the cochlear vessels or the supplying vessels of the cochlea. Additionally, the SG nerve fibers that cause these effects do not pass through the superior cervical ganglion.

KEY WORDS — cochlear blood flow, guinea pig, laser-Doppler flowmetry, sympathetic nervous system.

INTRODUCTION

Control of cochlear microcirculation has been attributed to systemic blood pressure (BP), neural influences, hemodynamics, and metabolic factors.[1] The role of the autonomic nervous system in the regulation of cochlear blood flow (CBF) has long been of interest to otologic researchers.[2] This topic has not been well addressed by physiologic studies, because of the many technical challenges in the development of precise, unambiguous measures of CBF and the methodology required for appropriate stimulation.[3]

Lorente de No[4] and Smith[5] clearly demonstrated autonomic nerve fibers to the blood vessels of the inner ear. Spoendlin and Lichtensteiger,[6] using histochemical techniques for staining catecholamines in the inner ear, demonstrated one system of fibers terminating on vessels within the modiolus and another that extended more laterally in the cochlea but remained independent of the blood vessels of the lateral wall. These findings have been supported by electron microscopic investigations by Densert and Flock.[7,8] In addition, immunohistochemical studies have indicated the presence of adrenergic transmitters in the inner ear.[9,10] Using a stain for tyrosine hydroxylase as an improved technique to describe the catecholaminergic innervation of the cochlea, Brechtelsbauer et al[11] found fibers positive for tyrosine hydroxylase along both radiating arterioles and radial collecting venules.

With intravital microscopy, Seymour[12] found constriction of the arterioles following the local application of 1/10,000 adrenaline and noradrenaline through the lateral wall fenestra. In addition, Seymour reported that prolonged sympathetic stimulation produced a marked concavity of Reissner's membrane on the stimulated side that suggested a decreased secretion of endolymph secondary to a decreased blood flow. In microsphere studies, Hultcrantz et al[13] reported a 25% decrease in CBF caused by superior cervical sympathetic stimulation.

Using a new approach in which adrenergic agents

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Supported by National Institutes of Health grant DC-00105 and the National Natural Science Foundation of China. The work was done during a World Health Organization fellowship period (T.R.). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Michigan.

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were applied directly to the round window, Ohlsén et al[14] reported CBF changes produced by the vasoconstrictive influence of local epinephrine and norepinephrine. With intravital fluorescent microscopy, Carrasco et al[15] observed arteriolar constriction in response to adrenergic drugs applied by continuous perfusion through the retrograde-cannulated right carotid artery at very low infusion rates. Most recently, Ren et al[16] have demonstrated a CBF reduction in response to electrical stimulation of the superior cervical ganglion (SCG); and Laurikainen et al (unpublished data, 1992) found a 10% to 15% decrease in ipsilateral CBF caused by electrical stimulation of the stellate ganglion (SG). Considered together, these results support the role of the sympathetic nervous system as a mechanism of CBF control. However, regarding the importance of sympathetic control and the origin of sympathetic fibers innervating the cochlear vessels, previous results are often conflicting or ambiguous. The purpose of the present investigation was to assess the role of electrical stimulation of the SG in CBF control, including the bilaterality of CBF control. Also, we describe a unique operative approach that permitted exposure of the ganglion without a thoracotomy.

MATERIALS AND METHODS

Animals and Operative Approach. Fifteen healthy young pigmented guinea pigs weighing 240 to 380 g were used in this study. After diazepam (5 mg/kg, intraperitoneally) was administered as a tranquilizer, analgesia was induced by fentanyl citrate (0.32 mg/kg, intramuscularly). An operative level of anesthesia was maintained by a supplementary half-dose of fentanyl every 30 minutes and a half-dose of diazepam every 2 hours. The head of the animal was placed in a heated head holder and a tracheotomy was performed to ensure free breathing. The left or right carotid artery was cannulated in a retrograde fashion for continuous BP measurement. The rectal temperature of the animal was maintained at 38°C ± 1°C with a servoregulated heating blanket.

After the cartilaginous tip of the sternum and part of the sternocleidomastoid muscle were removed, a tunnel was made between the trachea and common carotid artery and the ventral surface of the longus colli muscle on the ventrolateral aspect of the vertebral column. Microforceps were used to separate the soft tissue and enlarge the surgical field under the operating microscope. Usually, the sympathetic trunk was found in this location. As the tunnel passed caudally, at approximately the level of the first rib, a small fusiform enlargement could be identified as the middle cervical ganglion. Caudal to this level, at the level of the third or fourth rib, a third larger ganglion was found: the cervicothoracic ganglion or SG. The ganglion was gently separated from the ventrolateral surface of the longus colli and ventral capitis muscles. The bipolar intraneural electrode was then inserted into the center of the ganglion. After it was confirmed that the 0.25 mA stimulus of the SG caused significant increases of BP and heart rate, the electrode was fixed in place and the tunnel was closed. During the operation, great care was taken to protect the sympathetic trunk, the vagus nerve, the parietal peritoneum, and the thoracic duct of the lymphatic vessels.

A ventral surgical approach was used to expose both bullae without cutting muscles or large vessels. A 2-mm-diameter hole was made in each bulla, and the cochlear mucosa was gently removed with a small cotton pledget prior to placement of the laser-Doppler recording probe. After the probes were properly placed on the lateral wall of the third turn of the cochleas, the bulla holes were closed by removing the retractors from the soft tissue.

Electrode and Stimulation. A custom-designed bipolar intraneural electrode was used to stimulate the SG. The electrode was made of two lengths of Teflon-insulated, 76-µm-diameter platinum-iridium wire encased in plastic tubing. Insulation (0.6 mm) was removed from one end of the wires and the tips were sharpened. After the SG was exposed, the electrode was inserted into the center of the ganglion and held in place by a suture to neighboring muscles.

The electrical stimulus was produced by a computerized pulse generator. Capacity-coupled, charge-balanced, biphasic pulses with 1-millisecond pulse width at six pulses per second were used throughout the study. Intensities of 0.1, 0.25, 0.5, 1.0, and 1.5 mA were used to stimulate the SG; the duration of each stimulation was 5 minutes.

Bilateral Recording of Cochlear Blood Flow. Laser-Doppler recordings were made from the third turn of the cochlea bilaterally. A light application of petroleum jelly was used between the tips of the laser probes and the bone of the cochlea to avoid a laser-Doppler signal shift caused by fluid or blood collecting around the probe tip. The laser-Doppler flowmeters PeriFlux Pf1d and PeriFlux Pf2B (Perimed Co, Stockholm, Sweden) were used in this study.

The output from a laser-Doppler flowmeter consists of a concentration factor multiplied by a velocity factor. The concentration factor relates to the number of Doppler-shifted photons, and the velocity factor relates to the average frequency shift of the backscattered light. In order to avoid the potential problem of underestimating the blood flow at higher concen-

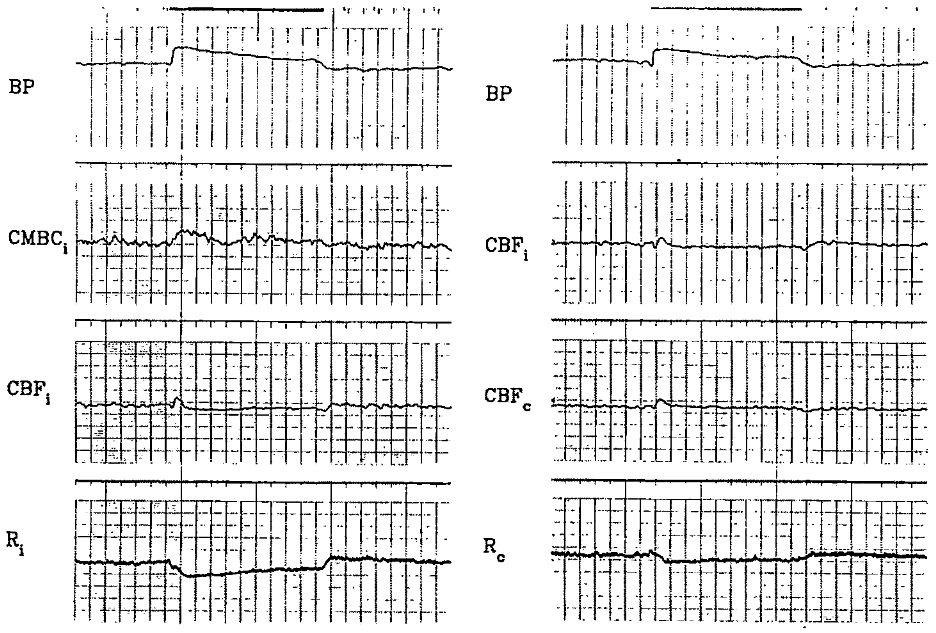

Fig 1. Raw data traces of BP, CBFi, Ri, CMBCi, Rc, and CBFc in response to sympathetic stimulation of SG from same animal. Stimulation was 0.5-mA biphasic pulses with 1-millisecond pulse width at six pulses per second. All parameters in right or left panel were recorded spontaneously. Bar on top of each panel indicates 5-minute stimulation duration. For all figures, see text for abbreviations.

trations, due to multiple scattering and homodyne effects, the concentration of moving blood cells (CMBCs) is provided as a signal output by laser-Doppler flowmeter PeriFlux Pf2B.[17] This CMBC value was recorded in the current study, along with measurement of CBF and BP.

Because of CBF's passive dependence on local perfusion pressure, which in turn is dependent on systemic BP, CBF oscillates somewhat following BP change. Thus, a change in CBF may reflect a combination of changes in the vascular resistance and changes in BP. In order to minimize the influence of systemic BP, the ratio of CBF/BP (R) was introduced in an earlier study[18] to approximate the conductivity of all upstream vessels that are in series with the measurement site and cochlear vessels. The percent change of the R value was calculated according to the formula

$$(CBF_0/BP_0 - CBF_t/BP_t)/(CBF_0/BP_0) \times 100\%$$

CBF$_0$ and BP$_0$ are baseline (BL) values of CBF and BP; CBF$_t$ and BP$_t$ are values of CBF and BP at time t.

Experimental Protocol. Five animals were stimulated at different intensity levels to determine the threshold and the relationship between the intensity and percent change in responses of BP, ipsilateral CBF (CBFi), and ipsilateral R (Ri), as well as the correlation between BP and CBFi. In 10 additional animals the effect of bilateral sectioning of the cervical sympathetic trunk below the SCG was examined by comparing the response to 0.5 mA stimulation before and after section. During stimulation, bilateral CBF and BP were recorded on a strip chart recorder (Hewlett Packard 7404A).

Data Analysis and Statistics. The average value over 1 minute immediately before stimulation was considered as the 100% BL, and data points were collected in 1-minute intervals across 5 minutes of stimulation and 3 minutes after stimulation. The percent values of the initial BL were then calculated. Data are presented as means and standard deviations of percentage of BL. Differences were analyzed with Student's two-tailed *t* tests.

RESULTS

All animals tolerated the operation well, and BP was maintained above 45 mm Hg throughout all experiments. The final set of data in the paper was collected within 4 hours of the induction of anesthesia. During this period, for each preparation the resting values of CBF, BP, and CMBC were stable.

Stimulation of 0.25 mA caused changes in BP and Ri in all five animals stimulated at this level. Stimulation of 1.5 mA caused significant contraction of the muscles in the vicinity of the SG, and this movement created an artifact on some CBF recordings. Because a stimulus of 0.5 mA in all preparations yielded a clear response, well below the level at which artifacts could be observed, this intensity was used primarily to evaluate the effect of sympathetic SG stimulation.

Typical responses of BP, CBFi, Ri, CMBCi, Rc, and CBFc caused by 0.5 mA stimulation are shown in Fig 1. The means and standard deviations calculated across animals and observations at 1-minute intervals during the 5-minute stimulations are shown in Fig 2. An example of clear changes in BP, CMBCi, CBFi,

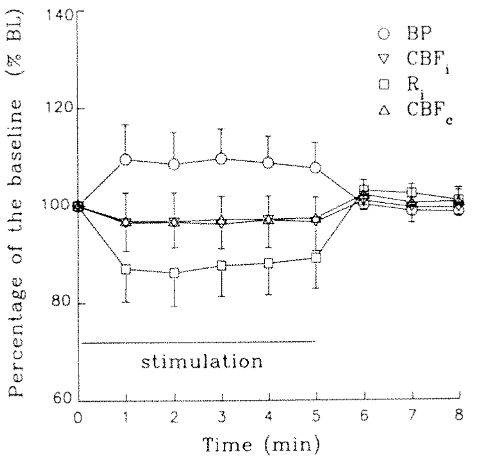

Fig 2. Responses of BP, CBFi, Ri, and CBFc to intraneural sympathetic stimulation of SG. Graph presents mean values and standard deviations. Sample numbers: BP 15, CBFi 15, Ri 15, and CBFc 13. Stimulation intensity and duration were 0.5 mA and 5 minutes.

and Ri is shown in the left column in Fig 1. The magnitude of evoked increases in BP and Ri is greater than the evoked decrease in CBFi. Following the onset of stimulation, BP and CMBCi increased and reached their peak values in less than 30 seconds, while CBFi and Ri demonstrated a gradual decrease. After an initial increase, BP tended to return toward BL but reached a plateau above it. Following termination of stimulation, BP generally fell somewhat below the BL and then recovered within a few minutes. The mean BP response to 0.5 mA stimulation was 108.7% ± 5.2% BL. Following onset of stimulation, CMBCi reached a maximum above BL within 30 seconds. The CMBCi then gradually returned to BL. The CMBCi in three of eight animals reached BL before the end of stimulation, and in five of eight animals CMBCi returned to BL within 1 minute after the end of stimulation. The average value of CMBCi was 123.5% ± 14.1% BL during the stimulation. With increased BP, CBFi first increased at almost the same rate as BP and then decreased despite a continued increase in BP. The CBFi reached its minimum value approximately 1 minute after the onset of stimulation and then remained stable until stimulation was terminated. The CBF of a few animals showed a slight tendency to return toward BL before the end of stimulation. Following the termination of stimulation, CBF recovered immediately with no significant overshoot. The mean of the CBFi changes was 96.5% ± 5.5% BL during stimulation. The Ri of each animal obviously shows a decrease, with a mean change to 87.8% ± 6.5% BL. The lowest value was reached about 1 minute after stimulation onset; Ri increased and recovered within a few minutes of stimulation.

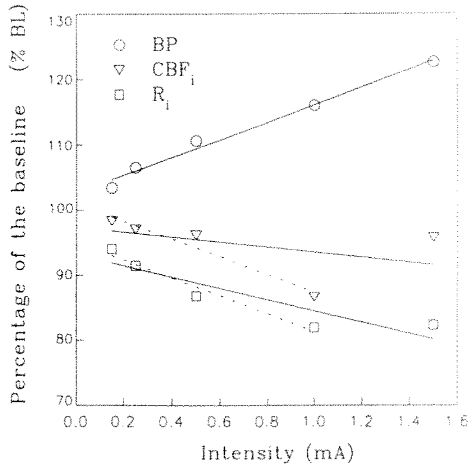

Fig 3. Correlation and regression analysis between intensity and values of BP, CBFi, and Ri. Differences of correlation coefficients were examined by *t* tests. Results of correlation and regression are as follows: BP and intensity, y = 102.66 + 1.1348x, r = .9928, p < .01; CBFi and intensity, y = 97.98 − 5.52x; r = −.6716; p > .05; Ri and intensity, y = 93.22 − 8.71x, r = −.9095, p < .05. If CBFi value in response to 1.5 mA stimulation is omitted, then for CBFi and intensity, y = 100.96 − 13.56x, r = −.9704, p < .05.

As shown in the right column of Fig 1 and in Fig 2, the contralateral CBF, CBFc, exhibited almost the same response as CBFi to 0.5 mA stimulation (96.9% ± 5.1% BL). The difference between CBFi and CBFc was tested, and no significant difference was found ($t = 5.9015$, $p > .05$). Thus, sympathetic stimulation of the SG can cause an equal bilateral change in CBF.

The relationships observed between the intensity of stimulation and the evoked changes in BP, CBFi, and Ri are shown in Fig 3. Using an assumption of linearity for the effect of electrical stimulation, we performed a linear regression analysis on the data. Although the BP data fit well, the apparent fit appears less than optimal for the relations of intensity to CBFi and Ri. This may reflect the contribution of a movement artifact to the laser-Doppler measurement at 1.5 mA stimulation. The dotted line gives the regression function with omission of the 1.5 mA data point ($r = .6716$, $t = 1.909$, $p > .05$).

Figure 4 shows a rather weak correlation between BP and CBFi ($t = 2.338$, $p > .05$) but an obvious tendency of a negative correlation between BP and CBFi. This negative correlation indicates that the CBFi response cannot be explained by either a passive property of the cochlear vasculature or an autoregulation mechanism of the cochlear vessels.

After the section of the cervical sympathetic trunk below the SCG, the 0.5-mA stimulation was repeated and caused CBFi to decrease to 97.1% ± 2.1% BL. No statistically significant difference ($t = 4.1674$, $p > .05$) was found between the data before (96.5% ± 5.5%) and after the section.

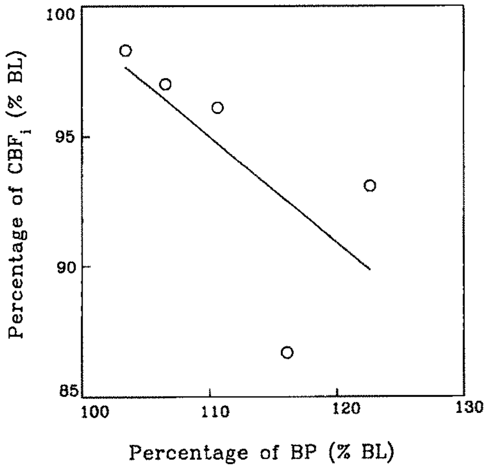

Fig 4. Correlation analysis between BP and CBFi ($y = 139.69 - 0.41x$, $r = .6718$). Result on *t* tests of correlation coefficient ($p > .05$) suggests poor correlation between BP and CBFi, but significant tendency of negative linearity was exhibited.

DISCUSSION

Inner ear blood flow is believed to be controlled by both local and systemic factors.[1] Although a nonlinear relationship between BP and CBF has been shown in a few studies, suggesting autoregulation of the cochlear blood vessels, BP definitely influences CBF, and CBF can show a passive dependence on systemic BP.[19-21] In a study of the effect of sympathetic input on CBF, it is difficult to avoid the influence of the general cardiovascular systemic effects on CBF, because the heart and most vessels of the body are innervated by the sympathetic nerves from the SG. Any manipulation, such as surgical or chemical sympathectomy, to eliminate sympathetic input to the heart and systemic vessels would cause changes in cardiac output and vessel resistance, which determine systemic BP and consequently affect CBF. Obviously, the CBF response to electrical stimulation of the SG, presented in this paper, reflects the sum effects of a direct sympathetically induced vasoconstriction, a change in local perfusion pressure reflecting the increased systemic BP, and autoregulation caused by increased local perfusion pressure.

The relationship between flow and pressure gradient in cylindric tubes is well known as Poiseuille's formula: $Q = Pr^4/8L\eta$, where Q is the flow, P is the difference in hydrostatic pressure between two points separated by a distance L, r is the internal radius, and η is the coefficient of viscosity. Under the experimental conditions of the present study, blood viscosity (η) and the length of the vessels (L) were constant. Only perfusion pressure and the diameter of cochlear vessels can cause CBF to change. In a study of the effects of myogenic responses in regulation of CBF, Brown and Nuttall (unpublished data, 1991) found a nonlinear pressure-flow relationship in the guinea pig cochlea. However, according to their study, BP and CBF should have a positive correlation. This is in contrast to the results (Fig 4) of this current study, which showed either no relation or a negative correlation. This decrease in CBF below the resting value cannot reflect the increased BP and local autoregulation in response to this increased pressure. The remaining possibility is that the decreased CBF reflects an increase in vessel resistance as a result of an electrically evoked decrease in vessel diameter. This interpretation is supported by the change in ratio CBF/BP, which indicates a decrease in vascular conductance during stimulation. The results of this study indicate that the sympathetic nerves from the SG play a direct and dynamic role in the control of CBF. These data are consistent with the recent study by Laurikainen et al (unpublished data, 1992) from our laboratory.

There are conflicting opinions regarding the origin of the sympathetic nerve supply to the cochlea. Using histochemical techniques, Spoendlin[22] concluded that there are two different types of adrenergic innervation of the inner ear: one innervation being strictly perivascular, originating in the SG, and the other being independent of blood vessels and originating in the SCG. However, Terayama et al[23] showed that all adrenergic fibers arising from the ipsilateral SCG course with the internal carotid nerve and along the internal auditory artery to the cochlea and vestibule, and terminate about vessels. In a recent study,[16] electrical stimulation of the SCG produced a rapid and significant decrease in CBFi, supporting Terayama's anatomic finding that perivascular adrenergic fibers also originate in the SCG. The current study demonstrates a limited response of CBF to electrical stimulation of the SG that is bilateral, consistent with the anatomic study of Spoendlin.[22] Thus, it appears that functionally the ipsilateral SCG is the primary source of sympathetic fibers controlling CBF; these fibers may have a close connection with the cochlear vessels. However, the SG appears to provide a bilateral source of sympathetic fibers that regulate CBF; these may have a loose connection with the cochlear vessels or innervate only the larger vessels of the cochlea. Considering the anatomic characteristics of the vertebrobasilar vessel complex, one possibility is that the SG sympathetic fibers proceed along the vertebrobasilar vessel system and overlap with the fibers from the opposite SG on the basilar artery.

The CMBC values showed a dramatic increase during sympathetic stimulation of the SG, indicating a hyperemia of cochlear blood vessels. It is possible that the systemic cardiovascular response to electrical stimulation is responsible for the CMBC increase. However, since the CMBC change is not proportional to BP or heart rate, another possibility is that the hyperemia may be caused by venous vessel contraction directly evoked by the electrical stimulation. One must also be aware that the CMBC output signal is not calibrated in an absolute or relative sense.

It has been found that resistance vessels reach a maximal contraction following electrical stimulation of the sympathetic nerves and then exhibit a tendency to return to BL in spite of continuous stimulation. Furthermore, after the termination of the stimulation the vessels dilate and the blood flow shows an overshoot. These phenomena have been defined as the "escape" phenomenon and "poststimulatory dilation."[24,25] The speed of the escape is different for individual organs, and the rate of the poststimulatory dilation is inversely related to the rate of the preceding contraction. We have demonstrated that the CBF response to electrical stimulation of the SCG exhibits a typical escape and poststimulatory dilation.[16] However, no significant escape or poststimulatory dilation were found in the present study, hence, that specific mechanism or site of action resulting in the observed CBF response to electrical stimulation of the SG may be different from that to stimulation of the SCG.

Moreover, compared with the results observed with stimulation of the SCG,[16] the CBF response to stimulation of the SG in the present study was slower and weaker. This difference in response of the vessels to sympathetic activation may reflect differences in the density and distribution of adrenergic innervation, their sensitivity, the relative magnitude of α- and β-receptor–mediated responses, the heterogeneity of adrenergic receptors and adrenergic receptor-coupling characteristics, or intrinsic vascular tone.[26] In general, the nerve-muscle relationship in the larger vessels is less intimate than in the smaller vessels. Changes in the nerve-muscle relationship in vessels of different sizes are associated with transmitter action.[27] Electron microscopic studies indicate that the distance from the cochlear vessels to the terminals of adrenergic fibers ranges between 1,000 Å and 3,000 Å.[8] Compared with the largest synaptic cleft separations (4 μm) reported in the dog pulmonary artery,[28] cochlear vessels have a very loose connection with the adrenergic nerve terminals. Spoendlin[22] found that the perivascular adrenergic fibers have no direct contacts with smooth muscle cells of the labyrinthine artery and no definite nerve endings, so that any sympathetic influence can occur only by diffusion of transmitter over some distance. It has been suggested that an effective influence can be exerted at a distance of about 1 μm.[29] Given the rate of diffusion of one quantum of norepinephrine in extracellular space,[30] and the location and density of termination sites, the transmitter around the cochlear vessels would be expected to be a lower concentration and would require more time to cover the longer distance between the adrenergic fiber and the affected cells of the cochlear vessels. Moreover, given the lower transmitter concentration around the terminal of the adrenergic fiber, the mechanisms of uptake into the varicosity and feedback control of transmitter release would be expected to play a less important role. This is consistent with the observation that the responses of the cochlear vessels to the electrical stimulation of the SG do not show a poststimulatory dilation or the escape phenomenon. These characteristics of CBF responses can provide direction for future pharmacologic and physiologic investigations of the mechanisms of sympathetic control of CBF.

Finally, we note that a number of clinical disorders of the inner ear have been presumed to reflect vascular disorders or an inadequate responsiveness of the cochlear vasculature to stress. Sensorineural hearing loss from Meniere's disease, presbycusis, some forms of intense noise exposure, and certain conditions of sudden hearing loss may depend to a significant extent on CBF.[2] Because of the lack of knowledge on the control mechanism of CBF, these disorders cannot be treated properly. The role of the sympathetic nervous system in the control of the cochlear microcirculation has been proven by CBF reduction and R decrease during electrical stimulation of the SG in this study. These findings can give some basis for the clinical treatment of some types of inner ear disorders. They certainly support the notion that the symptoms, and perhaps the cause, of some of these disorders may be exacerbated by environmental factors, diet, or drugs that affect the general physical and emotional stress level of the patient.

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PEDIATRIC SINUS ENDOSCOPY COURSE

The postgraduate Pediatric Sinus Endoscopy Course will be held June 10-12, 1993, at St Louis Children's Hospital, St Louis, Missouri. Participants should have taken a previous endoscopic sinus surgery course, and their practice should consist of a large group of pediatric patients. For further information, contact Marilyn Crawshaw at (314) 454-2138.

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DEVELOPMENT OF SECRETORY ELEMENTS IN MURINE TUBOTYMPANUM: LYSOZYME AND LACTOFERRIN IMMUNOHISTOCHEMISTRY

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Secretory activity, particularly of antibacterial agents such as lysozyme and lactoferrin, is an important aspect of the mucosal defense mechanism, and the development of these agents may have a direct bearing on the susceptibility of the ear to infection. In this study, the secretory cells of the murine tubal epithelium were first observed at gestational day 17. Although tubal glands began to develop on gestational day 18, their secretory activity was first shown on postnatal day 3. The number of secretory cells of the tubal epithelium increased rapidly immediately after birth, while that of the tubal glands showed a gradual increase from postnatal day 3. The epithelial secretory cells in the tubotympanum matured at birth, but the tubal glands matured gradually after birth. Lysozyme was first recognized in the epithelial secretory cells on postnatal day 1, while lactoferrin was first detected in the tubal glands on postnatal day 3. Both lysozyme and lactoferrin were co-localized in the serous cells of the tubal glands. The secretion of lysozyme and lactoferrin seemed to reflect the maturation of the secretory cells in the murine tubotympanum.

KEY WORDS — development, eustachian tube, immunohistochemistry, lactoferrin, lysozyme, middle ear, mouse.

INTRODUCTION

The eustachian tube and middle ear mucosal surfaces are protected by complex biologic defense mechanisms: mucociliary clearance, immune response, and secretory activity. Secretory activity is an important aspect of the mucosal surface defense mechanism. High concentrations of lysozyme and lactoferrin, which are considered to be antibacterial agents in mucosal secretions, have been detected in chronic middle ear effusions.[1-3] On the basis of an immunocytochemical study, Lim et al[4] suggested that lysozyme is secreted by middle ear mucosal epithelial cells in otitis media. They also determined that the antibacterial enzyme secretion is in a dynamic state, as a drastic increase of lysozyme was observed following middle ear infection. It is not yet determined whether this increase of antibacterial enzyme is parallel to the overall increase of the secretory cell population, or if it could perhaps reflect the preferentially increased production of secretory antibacterial substances (eg, lysozyme and lactoferrin). It is postulated that the protection of the middle ear mucosa from bacterial infection may be correlated with the development of the antibacterial secretory elements as well as the mucociliary system.

The morphology and immunocytochemistry of the secretory cells in the eustachian tube and middle ear have been described in both animals and humans.[5-10] Several authors[11-13] described the development of goblet cells and mucous glands in the eustachian tube in the human fetal temporal bone. Although the development of the goblet cells in rat middle ear was investigated by means of electron microscopy,[14] descriptions of their development as it relates to secretory activity in the tubotympanum have been limited.

A detailed study on the development of the secretory elements in the tubotympanum will be helpful in understanding how a mucosal defense system develops in the middle ear. The present study was undertaken to establish the development of secretory lysozyme and lactoferrin by the epithelial secretory cells, as well as the secretory glands of the tubotympanum, in developing mice by using Alcian blue–periodic acid–Schiff (AB-PAS) staining and lysozyme and lactoferrin immunohistochemistry.

MATERIALS AND METHODS

Thirty-four BALB/c mice, ranging in age from gestational day 13 through postnatal day 21, were used for this study. Gestational age was determined by the vaginal plug technique, using the approximate time of plug formation as day 1. All the specimens of differing ages were prepared for AB-PAS and immunohistochemical staining. After painless decapita-

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From the Otological Research Laboratories, Department of Otolaryngology, The Ohio State University College of Medicine, Columbus, Ohio. Dr Park is currently at the Department of Otolaryngology, Yonsei University College of Medicine, Seoul, Korea. This study was supported in part by a grant from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (DC00090). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Ohio State University.

REPRINTS — David J. Lim, MD, NIDCD/NIH, Bldg 31, Room 3C-25, 9000 Rockville Pike, Bethesda, MD 20892.

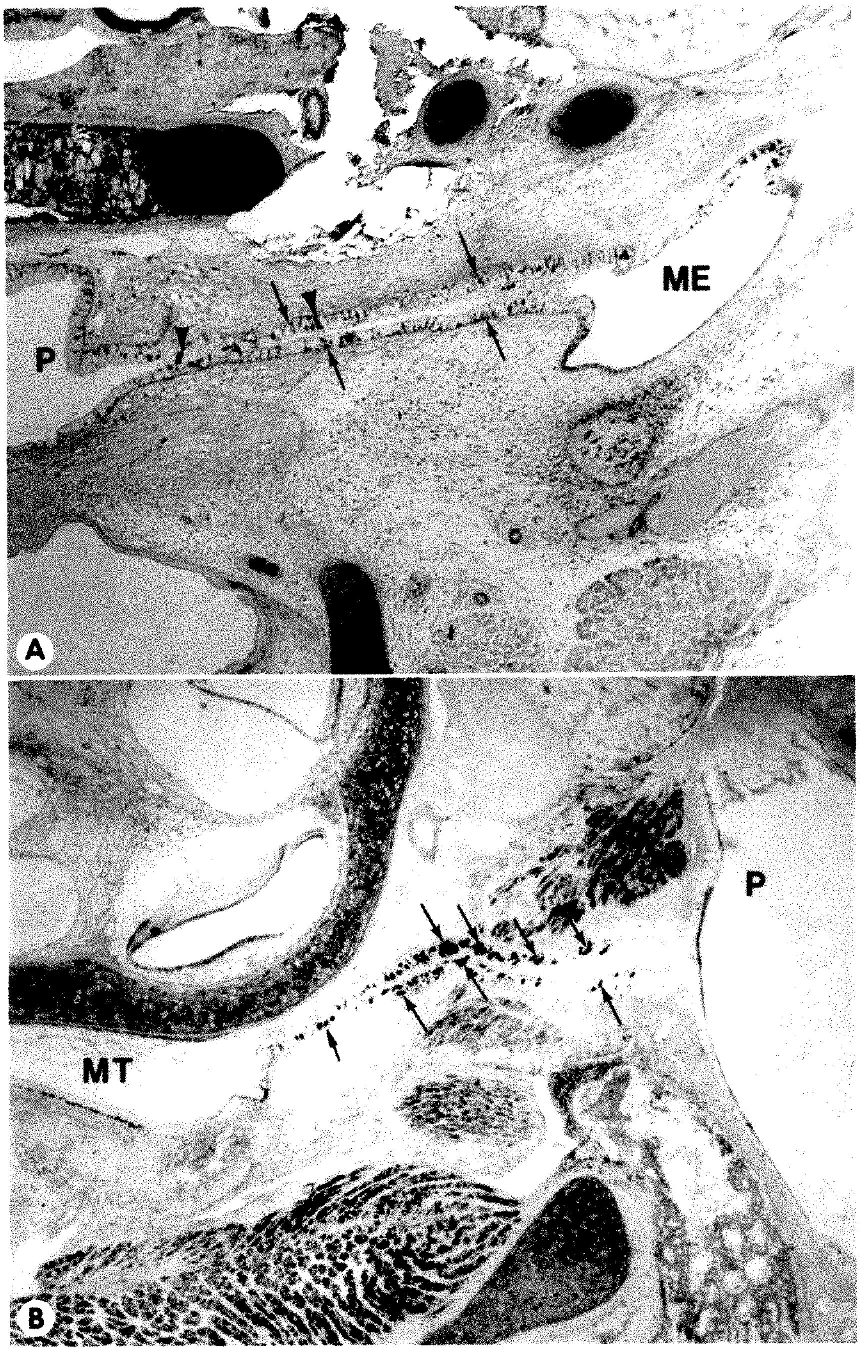

Fig 1. Coronal, AB-PAS, original x33. A) Tubal epithelial secretory cells with AB-PAS–positive (arrowheads) and only PAS-positive (arrows) staining are noted in 17-day gestational mouse. P — pharynx, ME — middle ear. B) Many secretory cells (arrows) are noted in tubal epithelium of 1-day-postnatal mouse. MT — mesenchymal tissue in middle ear cavity.

tion under inhalational anesthesia, the specimens were fixed by immersion in Z-Fix (aqueous buffered zinc formalin, Anatech Ltd, Battle Creek, Mich) for 2 days at room temperature. Postnatal specimens were decalcified with 10% ethylenediaminetetraacetic acid in 0.1mol/L Tris buffer (pH 6.95) for up to 2 weeks. Specimens were dehydrated and embedded in glycol methacrylate (JB-4; Polyscience, Warrington, Pa) at a cold temperature.

For immunohistochemical staining, 2.5-µm sections were etched with alcoholic sodium hydroxide solution for 20 minutes and were stained for lysozyme and lactoferrin by the avidin-biotin-peroxidase complex technique.[15] Briefly, etched and rehydrated sections were treated with 0.4% trypsin in 0.4% calcium chloride for 40 minutes at 37°C to enhance enzyme reaction. They were immersed in a solution of absolute methanol and 30% hydrogen peroxide at room temperature for 30 minutes to block endogenous peroxidase activity and then incubated in the following sequence of reagents at 37°C: 1) 20% normal goat serum for 30 minutes; 2) rabbit anti human lysozyme (DAKO, Denmark, lot 048) and lactoferrin (DAKO, lot 089), diluted 1:50 to 1:100, for 3 hours; 3) biotinylated goat anti rabbit antibodies

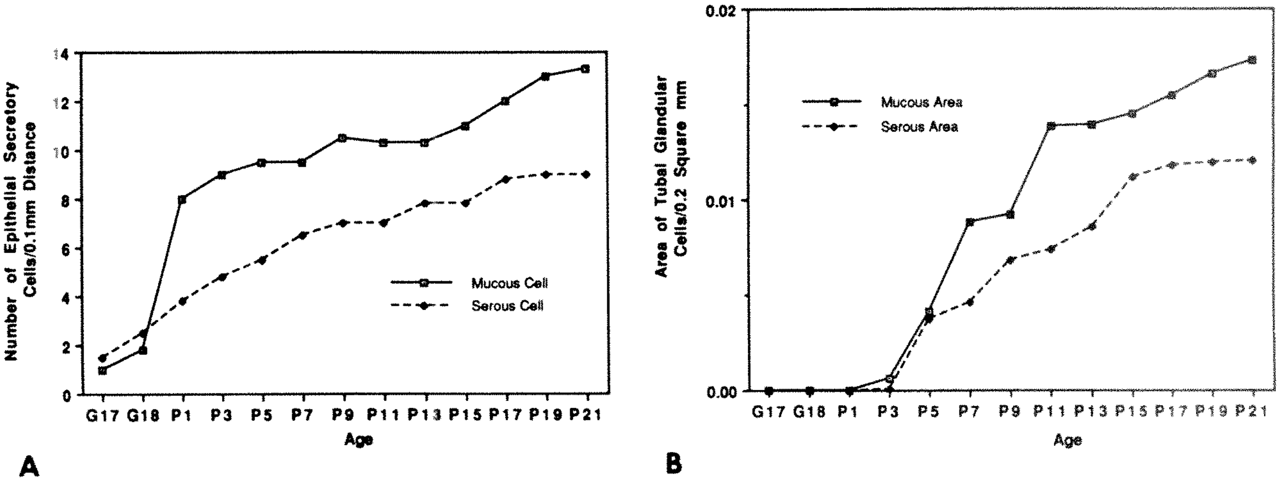

Fig 2. A) Incremental change of secretory cell number in tubal epithelium as function of age. Number of mucous cells increases drastically at postnatal (P) day 1, while that of serous cells increases gradually. During gestational (G) period, serous cells outnumber mucous cells. B) Incremental change of secretory cell area in tubal glands. Area of both mucous and serous cells shows gradual increment.

(Vector Laboratories, Burlingame, Calif) for 45 minutes; and 4) ABC-Elite kit (Vectastain, Vector Laboratories) for 1 hour. These steps, except for 20% normal goat serum, were alternated with rinses in 0.05 mol/L Tris-buffered saline for 10 minutes. All of the sera and immunoglobulins were obtained from a commercial source and diluted in Tris-gelatin antibody diluting solution. These sections were next incubated in freshly prepared 0.02 mol/L acetate buffered solution of 0.5% 3-amino-9-ethylcarbazole in N,N-dimethylformanide and hydrogen peroxide for 5 or 10 minutes. After being rinsed with this buffer, the slides were counterstained with hematoxylin. To demonstrate the specificity of the staining, negative controls were performed by replacing the primary antibodies with normal goat serum. For positive controls the trachea and small intestine of the mouse were examined.

For AB-PAS (pH 2.5) staining, the sections adjacent to the immunoperoxidase-stained sections were used to demonstrate mucosubstances of the secretory cells of the eustachian tube and middle ear. By this staining, carboxylated and sulfated acid mucosubstances stained blue, neutral mucosubstances stained magenta (serous cell), and a mixture of neutral and acid mucosubstances of the mucous cell stained purple.[16]

In order to study the occurrence of AB-PAS–positive (mucous) cells during development, we counted the number of stained cells at the epithelial lining of the pharyngeal portion of the eustachian tube, where sufficient secretory cells were observed. For convenience, the number of stained cells was expressed per 0.1 mm of distance. Because it was not possible to count the number of secretory cells in the tubal glands, the areas of mucous and serous cells per 0.2 mm^2 around the pharyngeal portion of the eustachian tube were traced under the microscope by using a digitizer. The lysozyme-positive cells in the tubal epithelium were counted and the areas of lysozyme- and lactoferrin-positive cells in the tubal glands were computed to derive the approximate ratio of immunostained cells to all secretory cells.

RESULTS

Before gestational day 15, no true line of demarcation was exhibited between the primitive middle ear cavity and the eustachian tube, as both are formed from the tubotympanic recess. Between gestational days 15 and 16, a definite division of the tubotympanic recess into the eustachian tube and the middle ear cavity was noted. At this age, epithelial secretory cells were not observed.

By gestational day 17, AB-PAS–positive cells were first observed in the tubal epithelium, although most of them were PAS-positive (Fig 1A). At postnatal day 1, both AB- and PAS-positive cells became numerous in the tubal epithelium (Fig 1B). The number of AB-PAS–positive cells in the eustachian tube epithelium drastically increased immediately after birth, while that of only PAS-positive cells increased gradually (Fig 2A).

However, no evidence of a tubal gland existed at gestational day 17. A few glandlike structures were later observed near the pharyngeal orifice of the eustachian tube in specimens from gestational day 18 and postnatal day 1, but they were not stained with AB-PAS (Fig 3A). Gland formation started first in the medial wall of the tube and started later in the lateral wall. Glands were laid down first at the pharyngeal orifice and gradually spread in the tympanic direction. By postnatal day 3, tubal glands positive for AB-PAS were first observed (Fig 3B), and they were prominent on postnatal day 5. In contrast to the

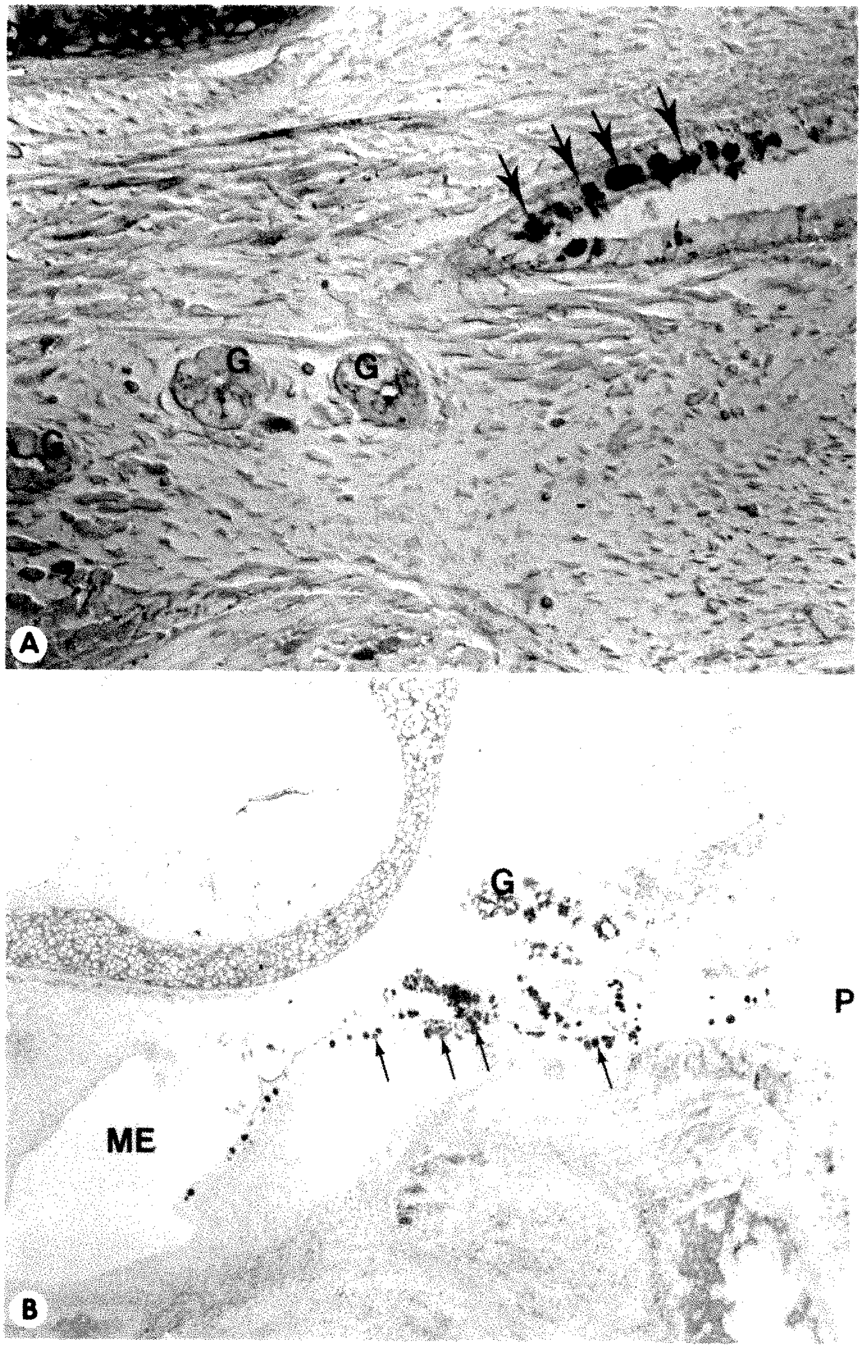

Fig 3. A) Some glands (G) with negative staining are recognized around pharyngeal orifice of eustachian tube in 1-day-postnatal mouse (AB-PAS, original x200). Epithelial secretory cells stained positive (arrows). B) Many AB-PAS–positive cells (arrows) were noted in tubal epithelium and glands (G) of 3-days-postnatal mouse (coronal, AB-PAS, original x33). P — pharynx, ME — middle ear.

tubal epithelium, the area of both AB-PAS–positive and PAS-positive cells in the tubal glands showed a gradual increase from postnatal day 3 (Fig 2B).

Both anti-human lysozyme and lactoferrin monoclonal antibodies used for this study cross-reacted with those of mice, as judged from the immunostaining patterns of the respiratory mucosa when compared with those of humans (see Discussion).

Depending on the enzyme concentration or antibody titers used, lysozyme- and lactoferrin-positive cells were stained from light to dark brown, but negative controls showed no reaction. At postnatal day 1, only lysozyme reaction was first observed in the epithelial secretory cells (Fig 4). However, lactoferrin reaction was first observed in the tubal gland at postnatal day 3 (Fig 5). Lysozyme- and lactoferrin-positive cells stained magenta in the sections stained with AB-PAS, indicating the presence of a neutral mucosubstance. Only serous cells of the tubal glands secreted both lysozyme and lactoferrin (Fig 6). However, lactoferrin was also detected in some mucous cells of the tubal glands, as well as in the serous glands (Fig 7).

In contrast to the tubal glands, lysozyme-positive

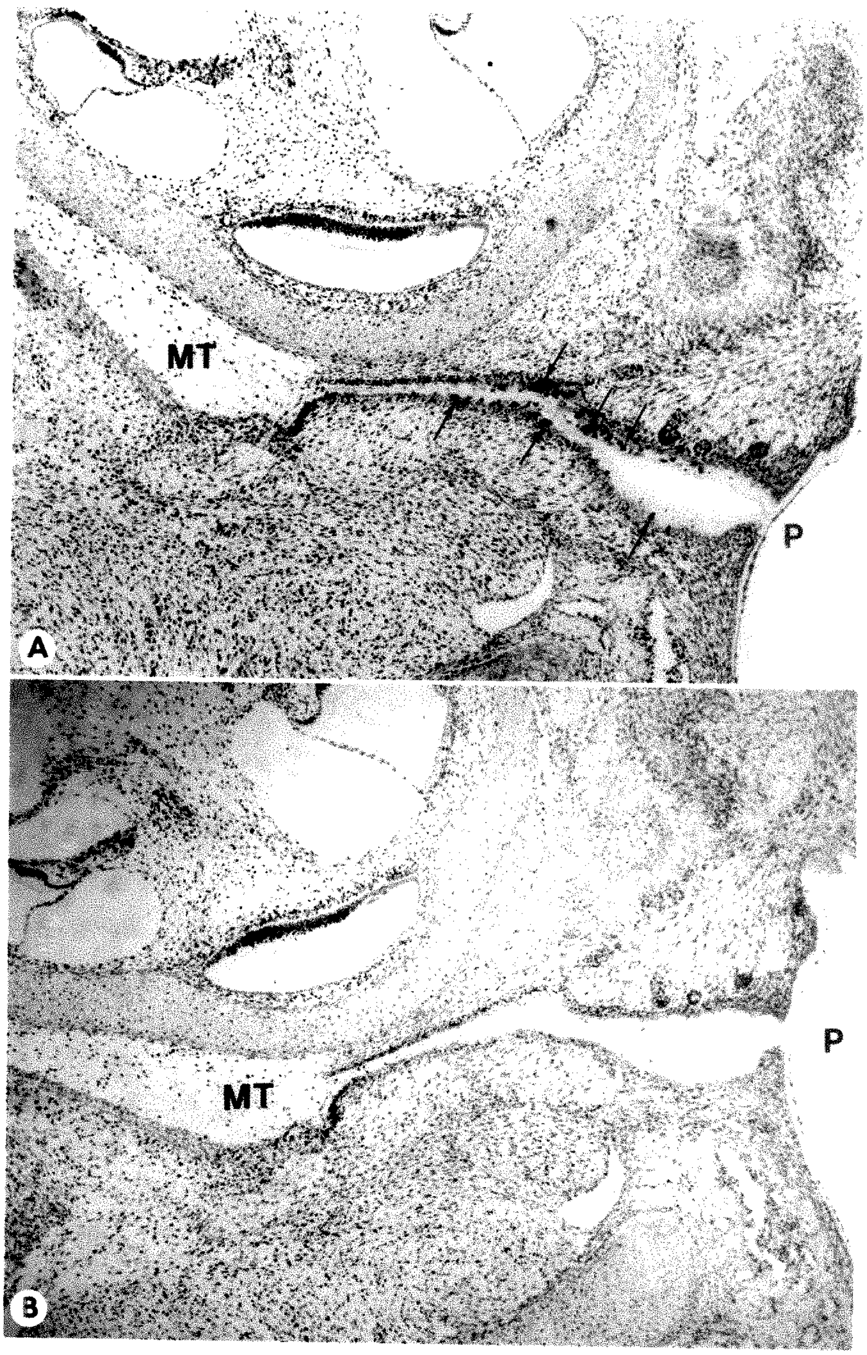

Fig 4. Coronal, ABC immunostaining plus hematoxylin, original x33. P—pharynx, MT—mesenchymal tissue in middle ear cavity. A) Same area as in Fig 1B, immunostained with antibody to lysozyme, shows positive epithelial secretory cells (arrows). B) Same area as in Fig 1B, immunostained with antibody to lactoferrin, shows no lactoferrin-secreting cells.

epithelial cells were found in some goblet cells of the eustachian tube and middle ear epithelium. Lactoferrin-positive cells were rarely seen in the tubal epithelium, but some goblet cells of the middle ear epithelium were positive for lactoferrin (Fig 8). In general, the goblet cells of the tubotympanal epithelium, if they were immunostained, had a stronger stain than the tubal glands.

To semiquantitate the production of the secretory antibacterial substances, we digitized the gland areas and computed the percentage of lysozyme- and lactoferrin-positive areas and AB-PAS–positive areas in the histologic sections. The percentage of lysozyme-positive areas was similar to that of lactoferrin-positive areas. Also, not all serous cells in the tubal glands secreted lysozyme and lactoferrin. Regardless of developmental age, roughly half of the serous cells in the tubal glands secreted lysozyme and lactoferrin, and about a third of the secretory cells in the tubal epithelium secreted lysozyme. Lactoferrin-positive epithelial cells were not counted, because they were rarely seen in the tubal epithelium.

In the trachea, used as a positive control, both lysozyme and lactoferrin were localized in the sub-

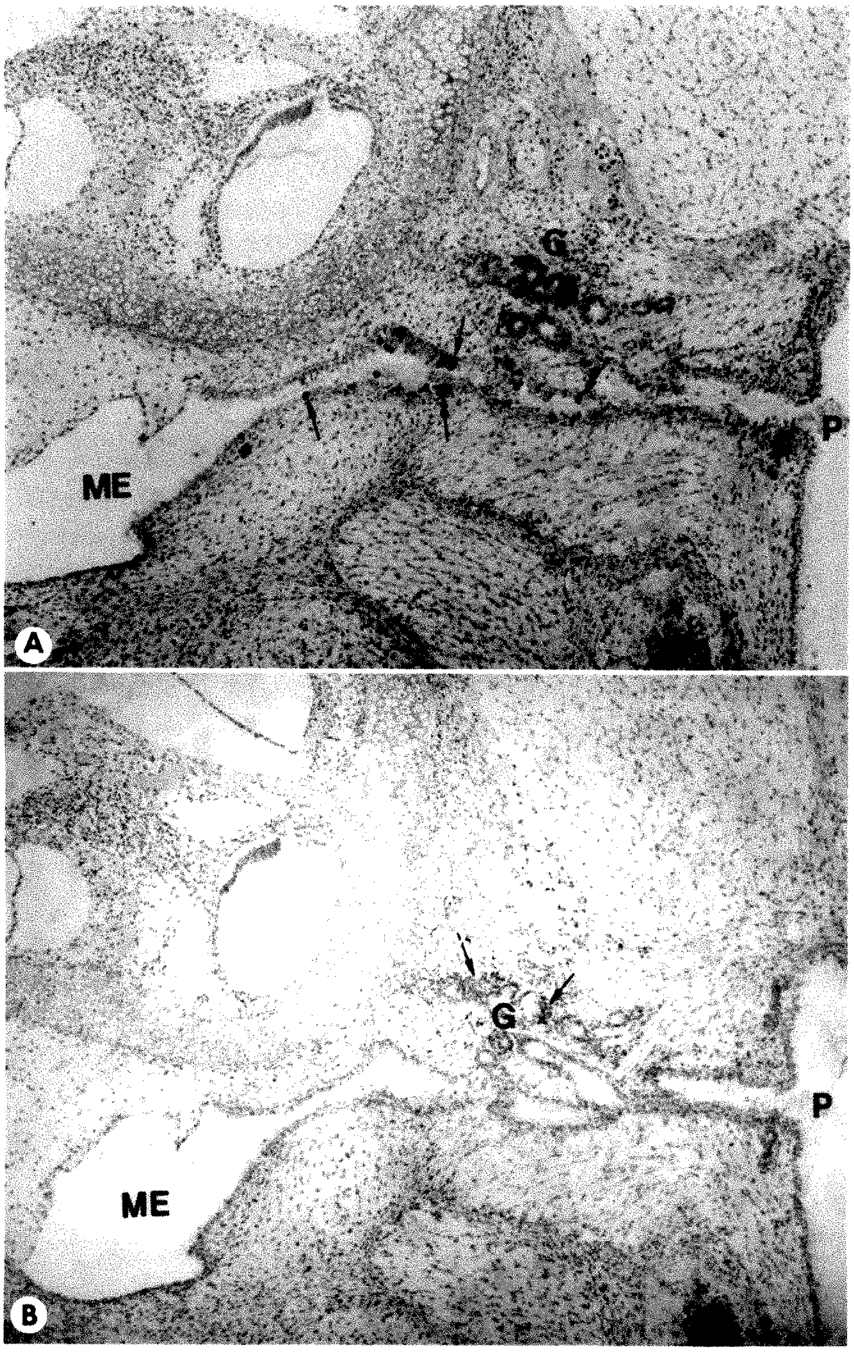

Fig 5. Coronal, ABC immunostaining plus hematoxylin, original x33. P—pharynx, ME—middle ear. A) Same area as in Fig 3B, immunostained with antibody to lysozyme, shows positive tubal glands (G). Some goblet cells (arrows) in epithelium are also labeled with lysozyme. B) Same area as in Fig 3B, immunostained with antibody to lactoferrin, shows positive tubal glands (arrows). No lactoferrin-secreting cells are found in epithelium.

mucosal glands, and only lysozyme was localized in some secretory cells of the mucosal epithelium (Fig 9). In the small intestine, lysozyme was localized in Paneth's cells, but no lactoferrin-positive cells were observed.

DISCUSSION

Development of the epithelial secretory cells in the tubotympanal cavity started at gestational day 17, but their biochemical maturation (evidenced by AB-PAS staining and the presence of lysozyme) began at postnatal day 1. Morphological development of the glands started between gestational day 18 and postnatal day 1, but they were first stained with AB-PAS, lysozyme, and lactoferrin at postnatal day 3. This finding implies that the biochemical maturation of the secretory cells of the tubal epithelium and glands occurs later than the morphological maturation. Another interesting observation was that the epithelial secretory cells appeared 1 or 2 days earlier than the tubal glands. This finding was different from that of a report on the human, in which the first glands were said to form in the tube a few days earlier than the epithelial secretory cells.[12] Although tubal secretory

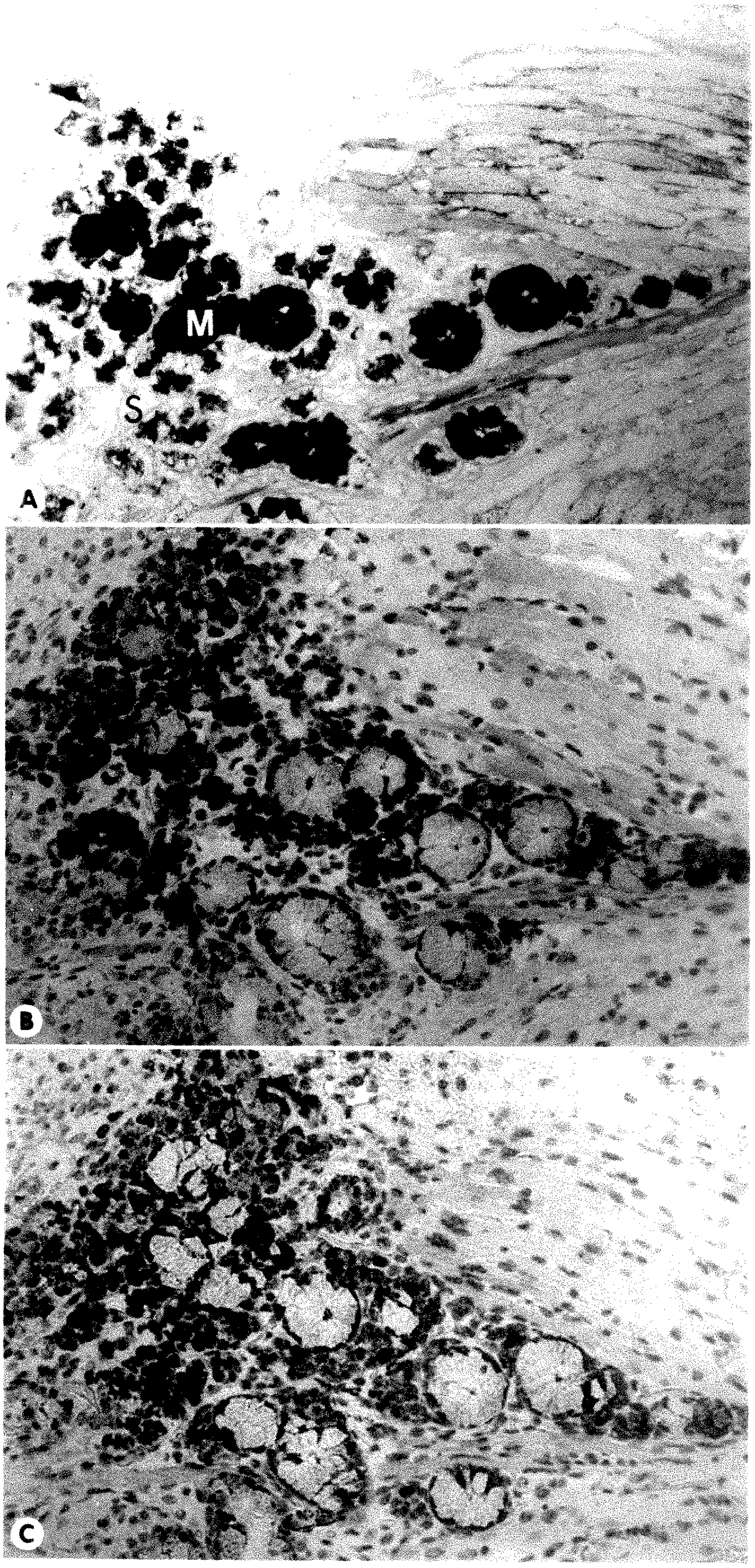

Fig 6. A) Tubal glands in 7-days-postnatal mouse shows serous (S) and mucous (M) parts (AB-PAS, original x200). B) Same area as in A, immunostained with antibody to lysozyme, shows that serous parts of glands, and not mucous parts, are positively stained (ABC immunostaining plus hematoxylin, original x200). C) Same area as in A, immunostained with antibody to lactoferrin (ABC immunostaining plus hematoxylin, original x200). Only serous parts of glands are stained.

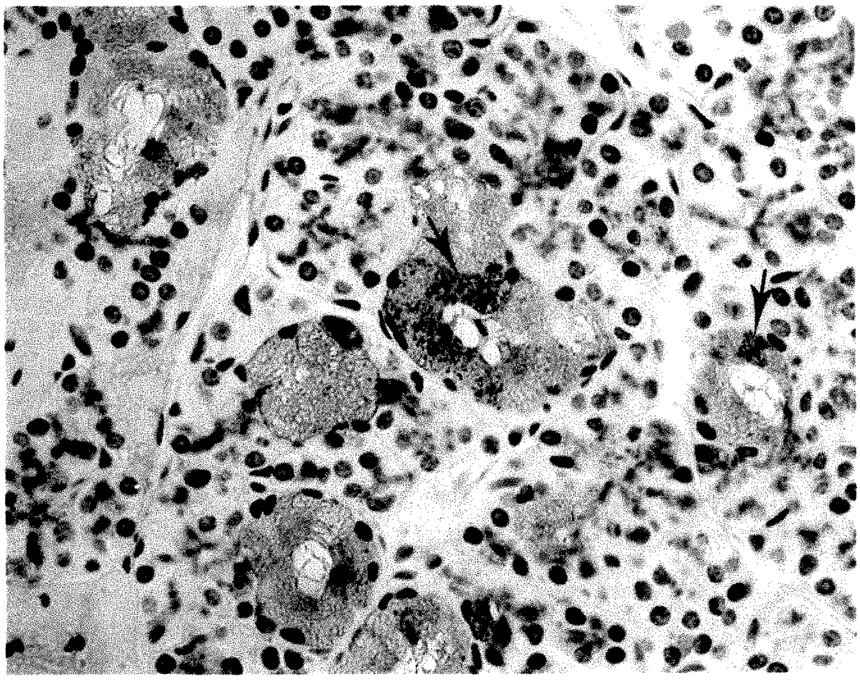

Fig 7. Some mucous parts of tubal glands, as well as serous parts, are labeled with lactoferrin (arrows; ABC immunostaining plus hematoxylin, original x400).

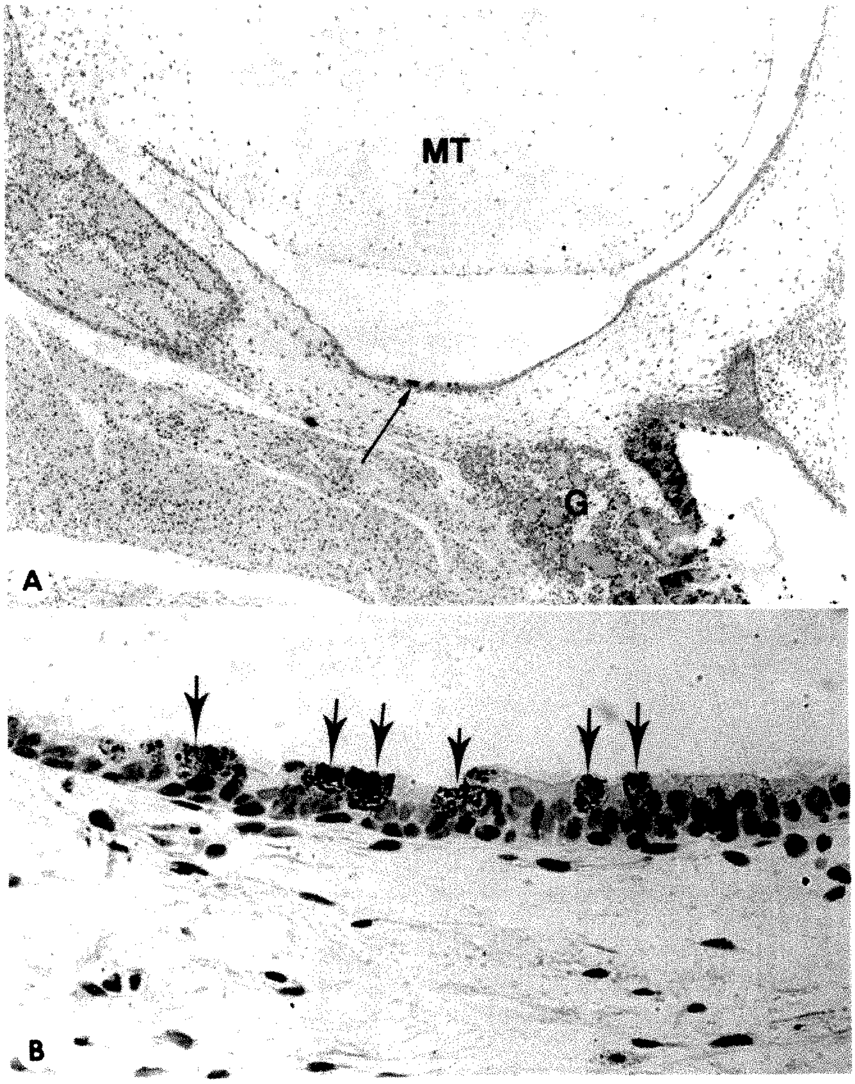

Fig 8. A) Some goblet cells positive for lactoferrin (arrow) are noted in middle ear epithelium of 7-days-postnatal mouse (ABC immunostaining plus hematoxylin, original x33). G — tubal gland, MT — mesenchymal tissue in middle ear cavity. B) Enlargement of A shows cells positive for lactoferrin (arrows) in middle ear epithelium (original x400).

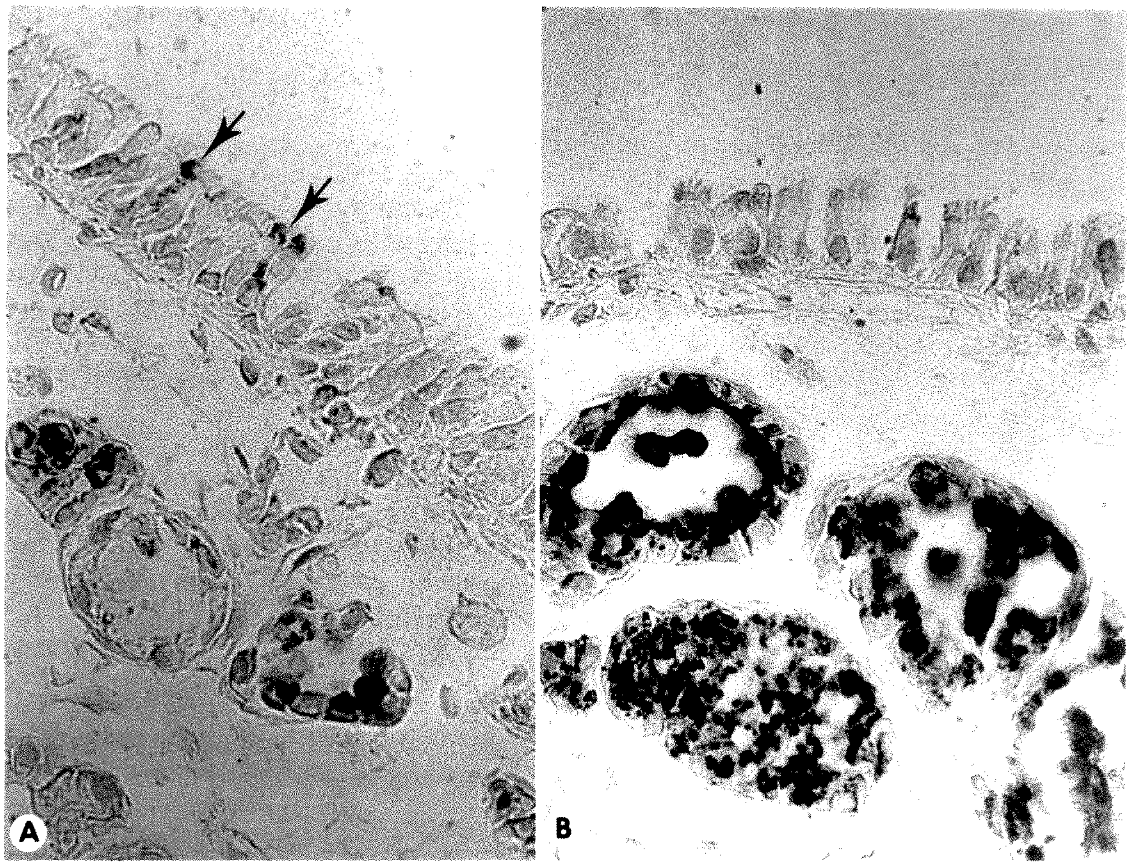

Fig 9. Sections of trachea (ABC immunostaining plus hematoxylin, original x400). A) Section shows lysozyme-positive cells in glands. Some goblet cells of epithelium are labeled with lysozyme (arrows). B) Another section shows lactoferrin-positive cells in glands.

cells begin to form during the gestational period, a dramatic increase of secretory cells and evidence of antibacterial secretory activity are observed after birth. This sudden increase in secretory activity of antibacterial substances coincides with the aeration of the tubotympanum after birth, and possible exposure to the respiratory bacteria that may have entered into the tympanic cavity when it was aerated.

Staining with AB-PAS has long been employed as a useful technique for the characterization of glycoproteins enabling identification of acid and neutral glycosaminoglycans.[17] Alcian blue is a highly selective stain for acid glycosaminoglycans, and the PAS-positive reaction is used for neutral glycosaminoglycans. Certain substances like mucins are reacted with both Alcian blue and PAS, yielding various shades ranging from purple to very deep blue. In this study, the secretory cells during their gestational period had PAS-dominant staining, but began to have AB-dominant staining after birth. Thus, AB-positive cells increased rapidly immediately after birth; this finding can be interpreted to mean that the mucinous components of secretory cells appeared with aeration of the lung.

The antibacterial secretory enzyme, lysozyme, is considered to be one of the most important mucosal defense mechanisms. The fact that lysozyme has been demonstrated in the middle ear and eustachian tube implies that it may also play an important role in protecting the tubotympanum.[4] In correlating the presence of lysozyme in the secretory cells of the tubal glands with AB-PAS staining, some interesting relationships become apparent. Serous parts of the secretory cells have been observed to be consistently associated with lysozyme and the presence of neutral mucosubstances, whereas mucous parts of the secretory cells are associated with lysozyme-negative and AB-PAS–positive acid mucosubstances.

The present finding of lysozyme in the serous parts of the tubal glands, and its absence from the mucous glands, was in agreement with findings in murine laryngotracheal glands,[18] the human nasal mucosa,[19-21] and the human tracheobronchial glands.[22-24] In contrast to this result, Hanamure and Lim[15] demonstrated that lysozyme was localized in the mucous cells of the chinchilla tubal glands. It is possible that these different results are due to species differences.

Lactoferrin is an iron-binding glycoprotein in milk and other external secretions. Several authors observed this protein existing in the glands, but not in the epithelial linings of the human bronchial mucosa,[25] the human nasal mucosa,[26] or the human salivary glands.[27] Mogi et al[28] also observed that lactoferrin was detected, not in the eustachian tube epithelium, but in the serous parts of eustachian tube glands of the guinea pig. Our study generally agrees with these observations. However, in our study, some cells of the tubal epithelium and some tubal mucous glands were stained positive for lactoferrin. It is very interesting that some goblet cells, especially in the middle ear epithelium and the tympanic portion of the eustachian tube, and some tubal mucous glands produce lactoferrin in the mouse.

Our laboratory earlier suggested that there are functionally different secretory cells: dark granulated (serous), light granulated (mucous), and mixed. Through lectin-gold cytochemistry, Ueno and Lim[29] recently demonstrated that the epithelial dark granulated secretory cells produce serum-type glycoprotein in the bony part of the chinchilla eustachian tube and the middle ear cavity, and that the light (mucous) granules of the glandular mucous cells and goblet cells in the chinchilla tubotympanum have serum-type glycoprotein in their dark cores. Our finding showing that lactoferrin is localized in some goblet cells and some part of the tubal mucous glands, as well as in the tubal serous glands, is consistent with the above observations. This finding may indicate the immunohistochemical heterogeneity of the glandular mucous cells and goblet cells.

In conclusion, the secretory cells in the murine tubotympanum function actively immediately after birth, although the mucociliary defense system starts to develop during the fetal stage, and the appearance of lysozyme and lactoferrin reflects the maturation of secretory cells in the tubotympanum.

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20TH INTERNATIONAL CONFERENCE ON COCHLEAR IMPLANTS

The 20th International Conference on Cochlear Implants will be held June 23-25, 1993, at the Ritz-Carlton Hotel, San Francisco, California. For further information, contact University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; (415) 476-4251.

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1993 CONFERENCE ON IMPLANTABLE AUDITORY PROSTHESES

The 1993 Conference on Implantable Auditory Prostheses will be held July 11-15, 1993, on the campus of Bryant College in Smithfield, Rhode Island. This is the sixth in a series of biennial research conferences originating with the 1983 Gordon Conference. The meeting will provide a forum for close interaction among scientists in all disciplines relating to the field of cochlear implants. For further information, contact Chris van den Honert, Division of Otolaryngology–Head & Neck Surgery, Box 3550, Duke University Medical Center, Durham, NC 27710; telephone: (919) 684-6099; E-Mail: chx@dukehrl.mc.duke.edu.

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IMAGING CASE STUDY OF THE MONTH

COMBINED (EXTERNAL AND INTERNAL) LARYNGOPYOCELE

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ADIR BABIACKI, MD

KFAR SABA, ISRAEL

In the normal larynx, the laryngeal ventricle is a fusiform fossa that lies between the true vocal cord inferiorly and the false vocal cord superiorly. The anterior part of the roof of the ventricle leads to a blind pouch termed the ventricular saccule or appendix. This sac is lined with pseudostratified epithelium containing mucous glands. A laryngocele is an air-filled dilatation of the ventricular saccule. A laryngeal mucocele is a fluid-filled laryngocele. This latter lesion, which is quite rare, results from proliferation of mucous glands within an obstructed laryngocele. Cases of superinfection, in which the mucous content is replaced by pus, are termed laryngopyocele (or laryngomucopyocele). Laryngoceles may be further classified according to their site of presentation. An internal laryngocele lies medial to the thyrohyoid membrane and is confined to the interior of the larynx. It usually presents as a swelling of the false vocal cord, extending toward the aryepiglottic fold. An external laryngocele protrudes through the thyrohyoid membrane via its neurovascular perforation and presents as a swelling in the neck. In the combined type of laryngocele, an internal laryngocele is associated with an external laryngocele. Laryngoceles may be unilateral or bilateral.

CASE REPORTS

Case 1. A 45-year-old man was urgently admitted with severe respiratory distress. He had a 6-month history of a slowly progressive swelling in the left side of the neck combined with respiratory difficulty, loss of appetite, weight loss, and severe snoring. Indirect laryngoscopy revealed a swelling of the left hemilarynx, obstructing the airway. The vocal cords could not be seen. On the left side of the neck, anterior to the upper third of the sternocleidomastoid muscle, there was an indurated smooth swelling. Because of the patient's severe respiratory distress there was no time for any further investigation, and an urgent tracheostomy was performed. This was followed by direct laryngoscopy, which revealed cystic bulging of the false vocal cord, and a provisional diagnosis of combined-type laryngocele was made. Marsupialization of the internal component of the cyst resulted in egress of a large amount of pus and disappearance of the cervical mass.

Two weeks later the mass reappeared. An axial computed tomography (CT) scan of the neck revealed a well-circumscribed cystic mass composed of a small intralaryngeal component and a larger extralaryngeal component in the left visceral compartment (Fig 1). The internal component caused thickening of the lateral laryngeal wall, with consequent narrowing of the airway. The external component caused displacement of the adjacent cervical structures. The patient underwent cervical exploration. A pus-containing cyst was completely dissected in one piece, including both the external and internal compartments. The patient was discharged following successful decannulation, and he is now, 18 months following surgery, free of symptoms.

Case 2. A 71-year-old woman was admitted because of progressive respiratory distress. During the previous 3 months she had complained of dysphagia and hoarseness. Three years earlier she had under-

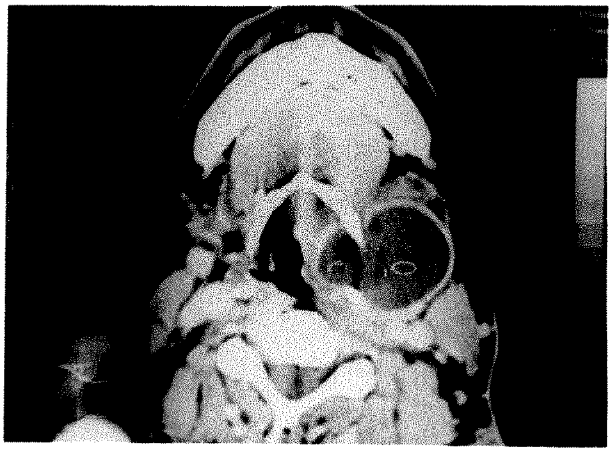

Fig 1. (Case 1) Axial contrast computed tomography at level of hyoid bone demonstrates homogeneous low-density bicompartmental (exolaryngeal [1] and endolaryngeal [2]) mass with rim enhancement involving both compartments.

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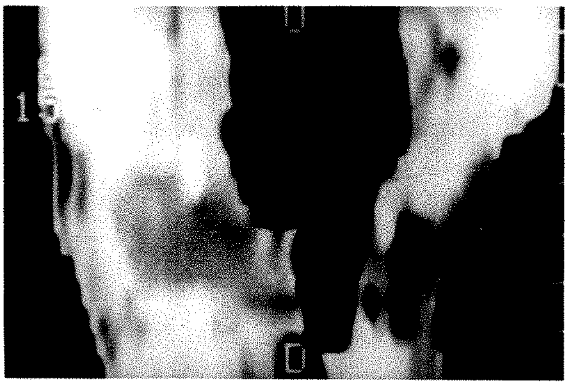

Fig 2. (Case 2) Reconstructed coronal section of larynx, demonstrating hypodense mass extending medial and lateral to thyrohyoid membrane and obstructing laryngeal airway.

gone endoscopic removal of a laryngeal cyst. A review of the surgery and pathology reports indicated that the procedure carried out at that time was marsupialization of an internal laryngomucocele. On admission, a soft neck mass was palpable in the right anterior cervical triangle. The patient's temperature was 38.2°C. Indirect laryngoscopy revealed a smooth submucosal swelling in the right hemilarynx, extending from the vallecula to the aryepiglottic fold and obscuring the right vocal cord. A CT scan revealed a cystic lesion located between the right hyoid bone and the thyroid cartilage (Fig 2). The cyst was composed of two compartments, medial and lateral to the thyrohyoid membrane. On operation the external component of a pus-filled cyst was identified at the level of the thyrohyoid membrane. The cyst was mobilized and its communication with the internal component was identified. The entire cyst was excised. Extubation was uneventful and there was no need for tracheostomy. One year postoperatively the patient is free of symptoms.

Case 3. A 69-year-old man suddenly developed stridor and respiratory distress while under chemotherapy treatment for transitional cell carcinoma of the bladder. On examination a cystic mass was palpated in the right anterior cervical triangle. In the larynx a smooth swelling was seen, extending along the lateral laryngeal wall from the vallecula down the aryepiglottic fold and causing glottic obstruction. Because of the deterioration in the patient's respiratory condition and since a combined-type laryngocele was suspected, we attempted to aspirate pus from the cervical mass, and succeeded in removing 25 mL, affording relief of airway obstruction. The patient was febrile (38°C), and intravenous antibiotics were started. A culture grew β-hemolytic *Streptococcus*. Five days later the cervical swelling reappeared and was again aspirated. Axial CT of the neck performed 1 week following the second aspiration revealed a large cyst composed of cervical and intralaryngeal components with an air-fluid level (Fig 3). Following 14 days of antibiotic treatment the patient was operated on and the cyst was completely removed via an external cervical approach. Six months later the patient is symptom-free.

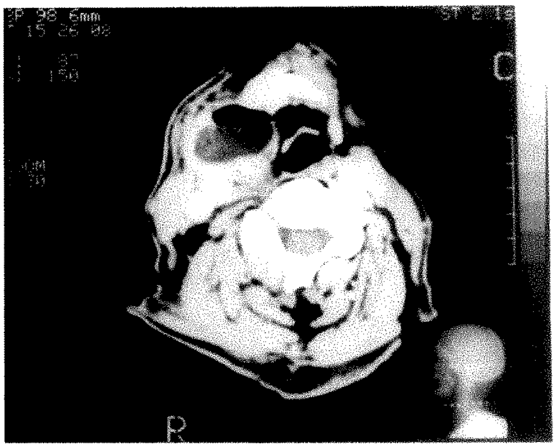

Fig 3. (Case 3) Axial contrast computed tomography in supraglottic area shows well-defined, hypodense mass with air-fluid level.

DISCUSSION

Laryngopyoceles are rarely encountered and their CT presentation has therefore received only limited attention. In one survey, laryngocele was found in 38 (12.5%) of 304 asymptomatic patients studied by CT of the larynx.[1] It thus seems that in many patients laryngocele can go undetected for a number of years. However, when proliferation of mucous glands causes obstruction of the laryngeal end of the saccule, a fluid-filled laryngomucocele develops that can become quite large and is usually symptomatic. Superinfection of a laryngomucocele causes a further increase in the size of the mass, often leading to an emergency situation.[2,3] This was the case in all three of our patients. The small number of reported laryngopyoceles suggests that laryngomucoceles rarely become infected; in one report the estimated rate of laryngopyocele superinfection was about 10%.[4]

The diagnosis of laryngopyocele is based on clinical and radiologic findings. The clinical differential diagnosis includes branchial cleft cyst, cystic hygroma, lipoma, paraganglioma, and lymphadenopathy. A lateral radiograph of the neck may show a well-circumscribed mass containing an air-fluid level. Conventional tomograms may show a connection between the cervical cyst and the laryngeal ventricle, but cannot clearly define the laryngopyocele. The appearance on CT of a well-marginated, smooth-contoured mass, with preserved overlying mucosa and no invasion of neighboring structures, suggests a benign lesion. Attenuation values of CT limit the differential diagnosis considerably. The characteristic location of the laryngopyocele adjacent to the hyoid bone and thyroid cartilage may also provide diagnostic assistance, and an air-fluid level, if present, further supports the diagnosis. On CT all three of our cases showed a well-circumscribed, homogeneously hypodense mass with peripheral rim enhancement, reminiscent of abscess.

The association of cancer of the larynx and laryngocele is well documented,[1,5] and an underlying neoplasm should always be excluded in such patients. Computed tomography may prove to be a useful tool for the accurate detection and prediction of the extent of tumor involvement within laryngoceles.

In contrast to previous recommendations,[2,3] in all three of our patients complete removal of the internal portion of the laryngopyocele was accomplished via a cervical approach without the need to resect a segment of the thyroid lamina.

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Ann Otol Rhinol Laryngol 102:1993

IMAGING CASE STUDY OF THE MONTH

OSTEOMA ARISING FROM THE STYLOHYOID CHAIN AND MANIFESTING AS A NECK AND OROPHARYNGEAL MASS

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INTRODUCTION

The styloid process and stylohyoid ligament are normal structures that rarely cause symptoms, even in patients in whom elongation of the process or ossification of the ligament is demonstrated. In 1937, Eagle[1] described patients who had pain in the oropharyngeal area, following tonsillectomies, that was presumably caused by the styloid process. The pain may radiate to the middle ear and mastoid region. There is a feeling of a foreign body sensation and difficulty swallowing, and the styloid process can be palpated on intraoral examination. Following the original description, the described clinical symptoms and findings have been referred to as Eagle's syndrome.[1-3]

There are various other syndromes associated with the stylohyoid apparatus, such as the carotid artery syndrome,[2-4] the stylohyoid syndrome, and pseudostylohyoid syndrome.[5]

Numerous case reports on these syndromes have appeared in the literature.[1-15] Pain of the head and neck region is the principal complaint in these syndromes. It is the purpose of this report to describe a case of osteoma arising from the stylohyoid chain that manifested as a mass in the neck and oropharynx.

CASE REPORT

A 63-year-old man was seen in the emergency room with a complaint of nasal speech without nasal congestion or respiratory distress. Examination of the neck revealed a firm mass, 1 cm in diameter,

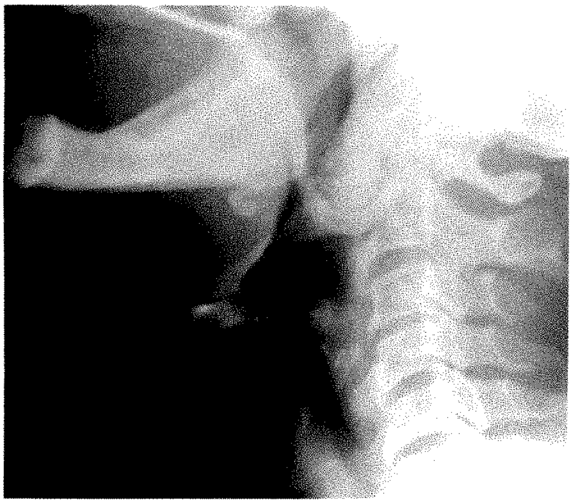

Fig 1. Lateral film of neck revealing ossification of stylohyoid ligament with extension from stylomastoid foramen to hyoid bone. There is osteoma at middle third of stylohyoid chain, adapting to forklike widening of adjacent ossified stylohyoid ligament.

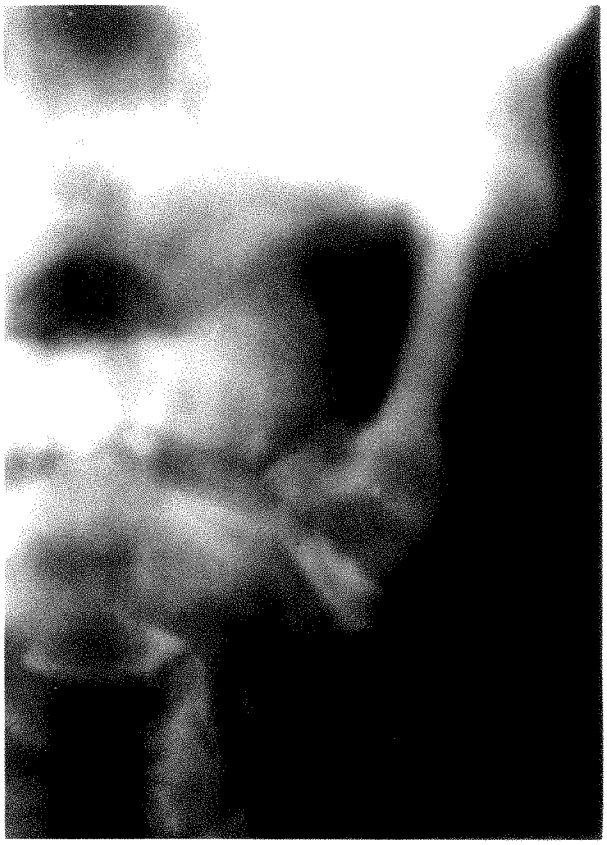

Fig 2. Lateral tomographic section through stylohyoid chain showing osteoma arising from lower end of styloid process. Note forklike configuration of adjacent ossified stylohyoid ligament.

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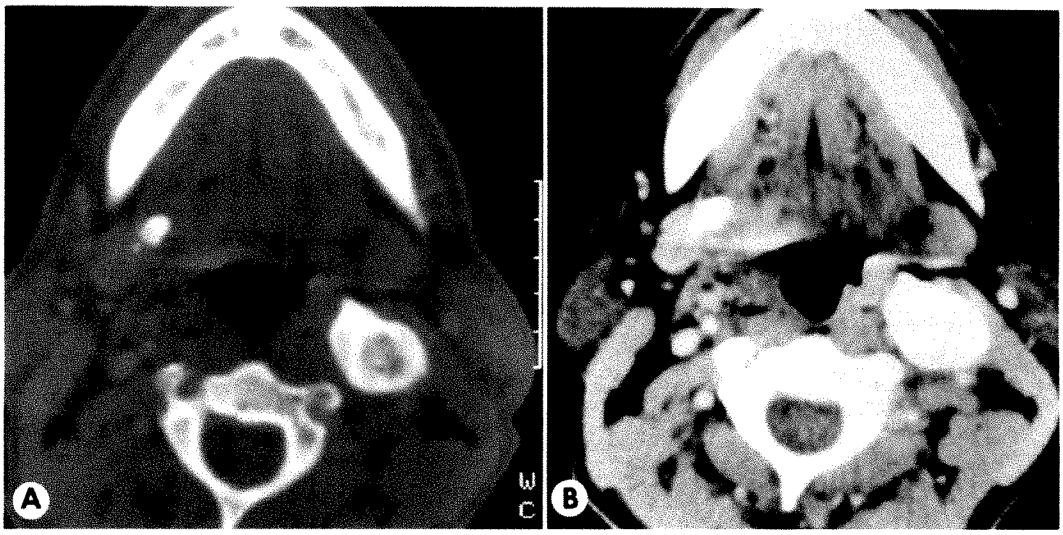

Fig 3. Axial computed tomograms. A) Bone window setting shows osteoma on left side. B) Soft tissue window setting shows slight bulge of oropharyngeal wall caused by adjacent osteoma.

between the mastoid process and the angle of the mandible. There was fixation of the larynx, which was immobile. On laryngoscopic examination, there was pooling of saliva in the left pyriform sinus. Examination of the oropharynx demonstrated a palpable mass on the left.

The lateral neck film revealed a long, enlarged styloid process with ossification of the stylohyoid ligament at its attachment to the hyoid bone (Fig 1). At the level of the angle of the mandible, a sharply defined bony mass, arising from the styloid process, was demonstrated (Fig 2).

An axial noncontrast computed tomography (CT) study was performed with bone and soft tissue window settings, with multiple 5-mm contiguous sections (Fig 3). The marked thickening of the styloid process and stylohyoid ligament was again demonstrated. An osteoma was seen to arise from the middle part of the stylohyoid chain at the level of the angle of the mandible. The osteoma was sharply defined, measured about 2 cm in greatest diameter, and projected into the paraoropharyngeal space. There was a bony exostosis of the lesser cornu of the hyoid bone at the insertion of the ossified stylohyoid ligament (Fig 4).

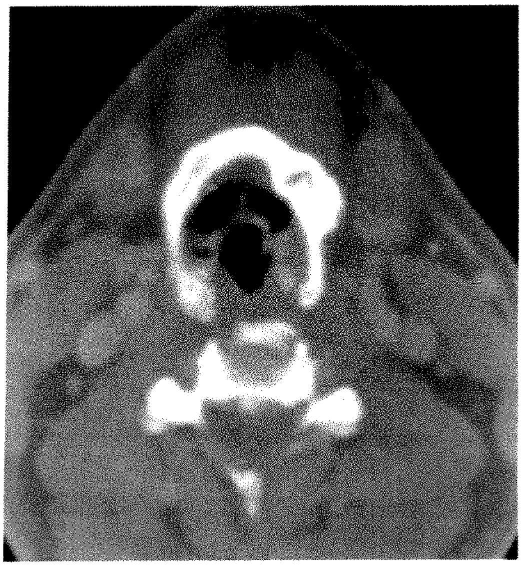

Fig 4. Axial computed tomogram (bone window setting) through hyoid bone revealing hypertrophic bone formation arising from hyoid bone on left.

DISCUSSION

The styloid process, stylohyoid ligament, and lesser cornu of the hyoid bone are formed by the second branchial arch of Reichert. Variation in ossification and fusion of the elements of Reichert's cartilage may occur.[16] Ossification of the preformed cartilage of the styloid process begins in the first or second year of life[17] and is completed by ages 7 to 8. The stylohyoid ligament, which is also preformed from cartilage, transforms from cartilage to connective tissue in the intrauterine stage.[18] The stylohyoid ligament retains its cartilaginous and osseous potential.[19] Changes in radiographic appearance of the stylohyoid chain are often erroneously termed calcification. Histologically, however, there is either hyperplasia of the styloid process or metaplasia of the stylohyoid fibrocartilaginous tissue into osseous tissue.[5] This is especially important in light of the presented case, in which an osteoma arose from an ossified stylohyoid chain.

The styloid process represents a bony projection from the base of the skull that courses downward, forward, and medially. The terminal part of the styloid process gives origin to the stylohyoid ligament, which extends inferiorly and forward to the lesser cornu of the hyoid bone. There is great variation in the length of the styloid process. Radiographic studies[6] have found a mean styloid length of 3 cm, which falls within the range of anatomic measurements (3 to 5 cm[20] or 1.5 to 4.8 cm[7]).

Dependent on different criteria in radiographic evaluation and patient selection, the incidence of ossification of the stylohyoid chain may vary from 2% or 4%,[21] to 28%,[6] to 89.4%.[22] However, there is indication of a positive correlation with age.[22] In a patient population with a mean age of 11 years, evidence of ossification was found in 40%.[8]

Ossification of the styloid ligament assumes various patterns. The ossification may begin at the lower end of the styloid process and extend inferiorly and continuously over a variable distance. There may also be an area of ossification that occurs as an isolated segment in part of the ligament with no connection to the styloid process. The transverse diameters of the ossified stylohoid ligament and the styloid process are variable.

The radiologic evaluation of the styloid process can be performed with a lateral neck film or a Panorex radiograph. On the lateral neck film, the upper half of the styloid process is difficult to visualize because of the overlying cervical spine. However, a long styloid process or the lower part of the stylohyoid ligament, anterior to the cervical spine from the angle of the mandible to the hyoid bone, is well illustrated. When slightly oblique films are obtained, usually the left stylohyoid process can be separated from its counterpart on the right side. The best radiologic modality for evaluation of the entire stylohyoid chain is a Panorex radiograph.

The stylohyoid process and ligament are demonstrated on axial CT sections with a bone window setting. In our case, the enlarged styloid process and the ossified stylohyoid ligament could be followed on contiguous axial sections from the base of the skull to the hyoid bone. Moreover, the osteoma was well demonstrated, as was its relationship to the adjacent structures, especially the parapharyngeal space.

The immobility of the larynx that was demonstrated on otolaryngologic examination can be explained by the fixation of the hyoid bone by the styloid chain. Elevation of the larynx is usually accomplished in conjunction with elevation of the hyoid bone. There was also some elongation and thickening of the styloid process on the right side.

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PATHOLOGY CONSULTATION

TALL CELL CARCINOMA OF THE THYROID GLAND

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Tall cell carcinoma of the thyroid gland is an aggressive variant of papillary carcinoma with a respectable 20% to 25% lethality. Its histologic features are characterized by a basal orientation of nuclei, abundant eosinophilic or oxyphilic cytoplasm, and a cellular height-width ratio greater than 2:1. These distinguish it from another aggressive variant, columnar cell carcinoma, which has a stratification of its nuclei and scant cellular cytoplasm.

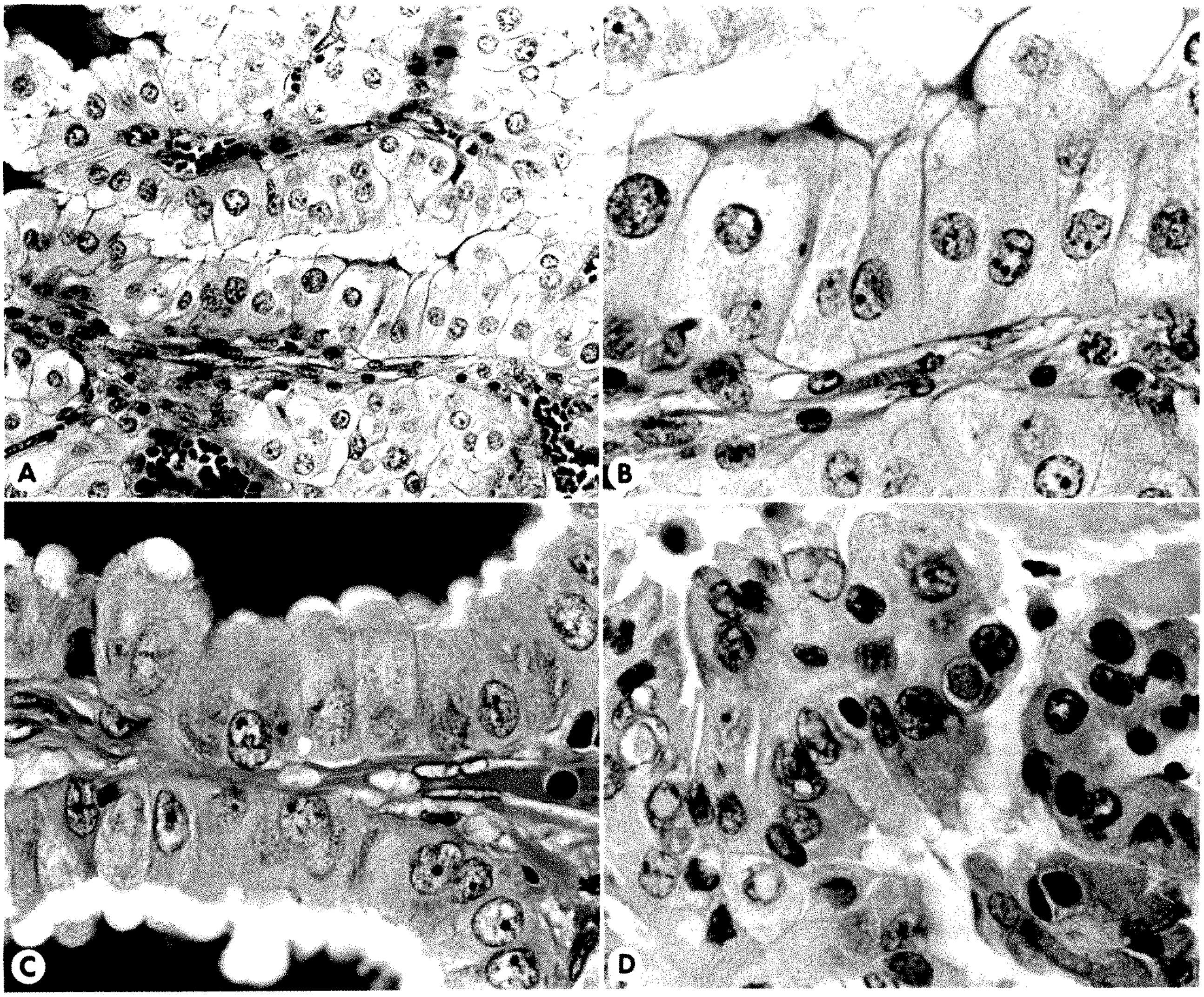

Fig 1. Tall cell carcinoma of thyroid gland. A) Regularly aligned tall cells arranged around empty spaces (H & E, original x120). B) Partial clearing of oxyphilic, granular cytoplasm in tall cells (H & E, original x280). C) Basal location of nonstratified nuclei of tall cell carcinoma cells (H & E, original x200). D) Prominent nuclear inclusions in cells of tall cell carcinoma (H & E, original x180).

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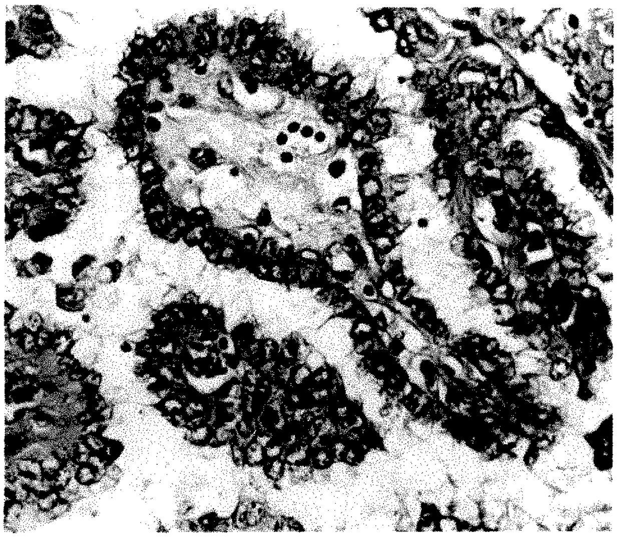

Fig 2. Conventional (non–tall cell) papillary carcinoma of thyroid gland (H & E, original x60).

Papillary carcinoma is the most common type of cancer of the thyroid gland. It manifests a histomorphologic heterogeneity so that several variants are recognized. The variants include follicular, encapsulated, diffuse sclerosing, columnar cell, and tall cell types. Some of these descriptors are inconsequential so far as biologic behavior is concerned; others are associated with significant prognostic implications and are therefore clinically important.

An infrequent variant of papillary thyroid carcinoma, tall cell carcinoma is associated with a locally aggressive growth and a shortened survival of its host.[1,2] Tall cell carcinoma was first described by Hawk and Hazard[1] in 1976. Eighteen of 193 (9.3%) patients with papillary carcinomas of the thyroid gland treated at the Cleveland Clinic from 1921 through 1960 had the tall cell variant. Whether this incidence is typical is not known, since no other institutional study has provided comparable data.

Tall cell papillary carcinomas of the thyroid gland are often large (>6 cm) neoplasms and have a conspicuously papillary gross pattern. The average age of patients is greater than that of patients with conventional papillary carcinoma. The sex ratio of patients is like that for papillary carcinoma in general and hence favors women.

The carcinoma's aggressiveness is manifested not only in its local invasion and recurrences, but also in its lethality. Johnson et al[2] recorded the following data: a 75% metastatic rate to cervical lymph nodes, a 42% extrathyroidal (cervical soft tissues) extension rate, a 58% local recurrence rate, and a 17% incidence of distant metastases. In contrast to conventional papillary carcinomas, tall cell carcinoma has an excessive mortality. Hawk and Hazard[1] reported a 22% death rate, often within a few years after diagnosis. The carcinoma was life-consuming in 25% of the patients reported by Johnson et al.[2] Johnson et al further define tall cell carcinomas as papillary carcinomas in which at least 30% of the neoplasm has tall columnar cells with basally oriented nuclei. The cells have an eosinophilic to oxyphilic cytoplasm and a height-width ratio greater than 2:1. There may be a prominent clearing of the cytoplasm. The nuclei of tall cell carcinoma are basal in location, are often vesicular, and have nuclear grooves (Fig 1). A papilliferous architecture is typical, but foci of follicles can be found. Calcospherites are less often present than in the usual papillary carcinoma (Fig 2).

Another rare histologic variant of papillary carcinoma, columnar cell carcinoma, shares the aggressive behavior of tall cell carcinoma of the thyroid gland.[3] Coexpression of each of these variants has also been described.[4] The two purely descriptive terms used to define the two variants are yet again examples of surgical pathology's sometimes ambiguous terminology. Without knowing the unique histopathologic characteristics of a columnar cell carcinoma, one could justly ask what the difference is between a columnar cell and a tall cell. Columnar cell is, indeed, a poor term for a carcinoma that has high-grade histologic features. Papillary growth is less dominant than in tall cell carcinomas, and a solid and cribriform architecture is often present. The columnar cell is also distinctly different from the tall cell. There is a marked stratification of nuclei in the columnar cells, and their cytoplasm is scant. With these nuclear and cytoplasmic characteristics, the two variants should not be confused.

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BOOK REVIEW

Smell and Taste in Health and Disease

Thomas Getchell, Linda Bartoshuk, Richard L. Doty, and James B. Snow, editors. Hard cover, illustrated, indexed, 833 pages, 1991. Raven Press, New York, NY, $165.

A text of this nature has long been needed in the field of otolaryngology. Although the subject is by no means new, as well-documented research in chemosensation indicates, there has recently been a resurgence of interest in the clinical significance of smell and taste. This may be in part due to those in related fields, such as neurosurgery, oncology, and psychiatry, contributing to research being done in these areas. Certainly, these specialties and many more will benefit from answers obtained in the chemosensory research.

The text is divided into seven sections that contain chapters authored by some of the foremost people in this field, and may well represent the most current thinking in chemosensation. In their effort to present comprehensive coverage of this topic, in their foreword and preface the editors sum up the historical significance of chemosensory research and integrate the separate disciplines that continue investigations in this area.

The early sections of the book cover the necessary topics of phylogeny and neurobiology of the olfactory and taste systems. There is a complete discussion of both the physiology and embryology involved in both systems, as well as the importance of mucus and saliva as integral parts of olfaction and taste. These chapters are heavily weighted with research references that would serve as an excellent bibliography for further investigations of the topic. An especially interesting chapter is The Trigeminal System, by Wayne Silver and Thomas Finger, in which the authors differentiate the chemosensation of the trigeminal system from that of the olfactory system and explain how the two impact on each other. The acquisition of taste preferences normally aversive to humans, such as horseradish and chili peppers, is suggested to be a form of thrill-seeking.

Psychophysical Integration covers the interesting topics of taste perception and spatial relations, odor memory, and the chemical senses in aging. The assertion by Inglis J. Miller and Linda M. Bartoshuk that there is no specific gustatory localization for the classic bitter, sweet, sour, and salty tastes should be enlightening to those schooled in the topography of specific taste on the tongue. In addition, the debate as to whether or not age affects the chemosensory abilities is well discussed, although more research is required. The fact that some older individuals maintain keen chemosensation would lead to the conclusion that a deficit in smell and taste is not necessarily a natural consequence of aging.

Chemosensory Regulation of Behavior introduces chapters regarding the role of taste and smell in appetite, nutrition, and behavior. Flavor Aversion, by Ilene Berstein, sheds light on why cancer patients may develop aversions that further lead to cachexia and weight loss, and gives insights as to why alcoholics may differ from the normal population. Richard H. Porter discusses the role of odors as critical first cues in forming early mother-infant relationships, which may be essential in developing those social bonds necessary to sustain life.

The remaining three sections of the book are devoted to the clinical application of taste and smell research. Nasal airflow and obstruction, medical imaging, and differential diagnosis are well discussed. More important is the emphasis on the role of adequate history and physical examination, including endoscopic and telescopic examination of the nasal cavity. Marion E. Frank and David V. Smith author an interesting discussion on electrogustometry and its underutilization as a clinical tool for measuring taste thresholds.

The chapters on transport disorders stimulate interest in those specific disease processes that prohibit appropriate nasal airflow. While this section is fairly comprehensive, even to the point of including those cosmetic nasal procedures that can result in obstruction, there is nothing here that has not been previously reviewed in other otolaryngology texts. The difference lies in the emphasis on taste and smell. Especially germane at this time is April E. Mott's dicussion concerning topical steroid therapy in nasal polyposis. Her emphasis on the medical treatment of nasal polyposis should be well heeded because of the chronic nature of the disease state. Oral Conditions Affecting Chemosensory Function, by Frank A. Catalanotto and Edward A. Sweeney, relates the dental perspective in evaluating oral disease as a source of dysfunction. Covering topics such as periodontal disease, intraoral prosthetics, amalgams, and galvanic stimulation, this brief but thorough review emphasizes the need to carefully evaluate the oral health of the patient with taste dysfunction.

Three chapters are worth mentioning in the section Sensorineural Disorders. In Biopsy of the Olfactory Neuroepithelium, R. Casey Strahan, Bruce W. Jafek, and David T. Moran describe in detail how to obtain an adequate biopsy. It is hoped that useful information can be gathered by correlating the biopsy with clinical syndromes, especially in cases of Alzheimer's disease and Parkinson's disease. Head Trauma, by Richard M. Costanzo and Nathan D. Zasler, provides information on the pathophysiology and prognosis of smell and taste dysfunction following head injury. More important, they probe the issues of functional sequelae of posttraumatic anosmia, such as safety issues and hygiene matters. Lloyd M. Biedler and James C. Smith delve into questions that have puzzled many head and neck surgeons about their irradiation patients in the chapter Effects of Radiation Therapy and Drugs on Cell Turnover and Taste. Both irradiation and chemotherapy can induce conditioned taste aversions, changes in the salivary system, changes in blood chemistry, and changes in the oral epithelium. Thus, the anorexia seen with cancer and cancer treatment is multifactorial.

The final section of this text deals with systemic conditions that manifest as chemosensory dysfunction, and their treatment. This makes for interesting reading, but no novel ground is broached. The treatment of taste and smell disorders, which should have been fully explored, is only briefly reviewed in the chapter by Susan S. Schiffman, Drugs Influencing Taste and Smell Perception. Indeed, it is in their coverage of the clinical implications and treatment of smell and taste dysfunctions that the editors have fallen just slightly short of their intended goal of bringing full cycle the study of smell and taste. These aspects are not particularly well defined in this text, which is more heavily weighted toward basic science. That may well be the major deficit of this book, since the identification and treatment of chemosensory dysfunctions should be one goal of the practicing otolaryngologist.

Nevertheless, the formidable task of presenting a subject that increasingly draws interest, as the medical community becomes more aware of such complaints from patients, has generally been well handled by the editors. By organizing the book into sections, the editors have to a great extent overcome the obstacles incurred when presenting so many opinions on a number of topics. The end result is a book that otolaryngologists, neurologists, neurosurgeons, oncologists, and dentists should find more and more useful as a reference as knowledge of chemosensory dysfunction unfolds. It is to be hoped that in the second edition the area of treatment will take a greater role.

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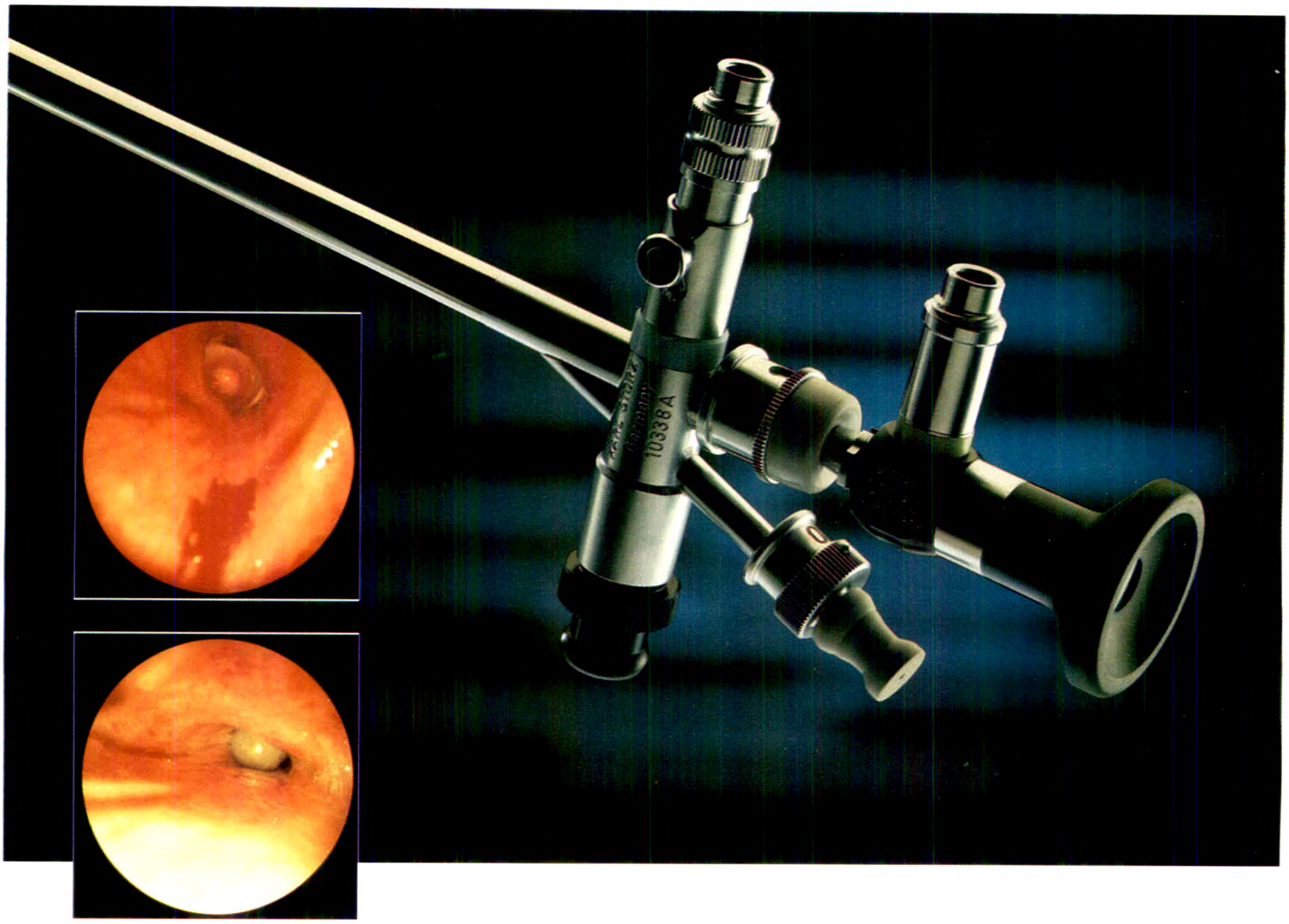

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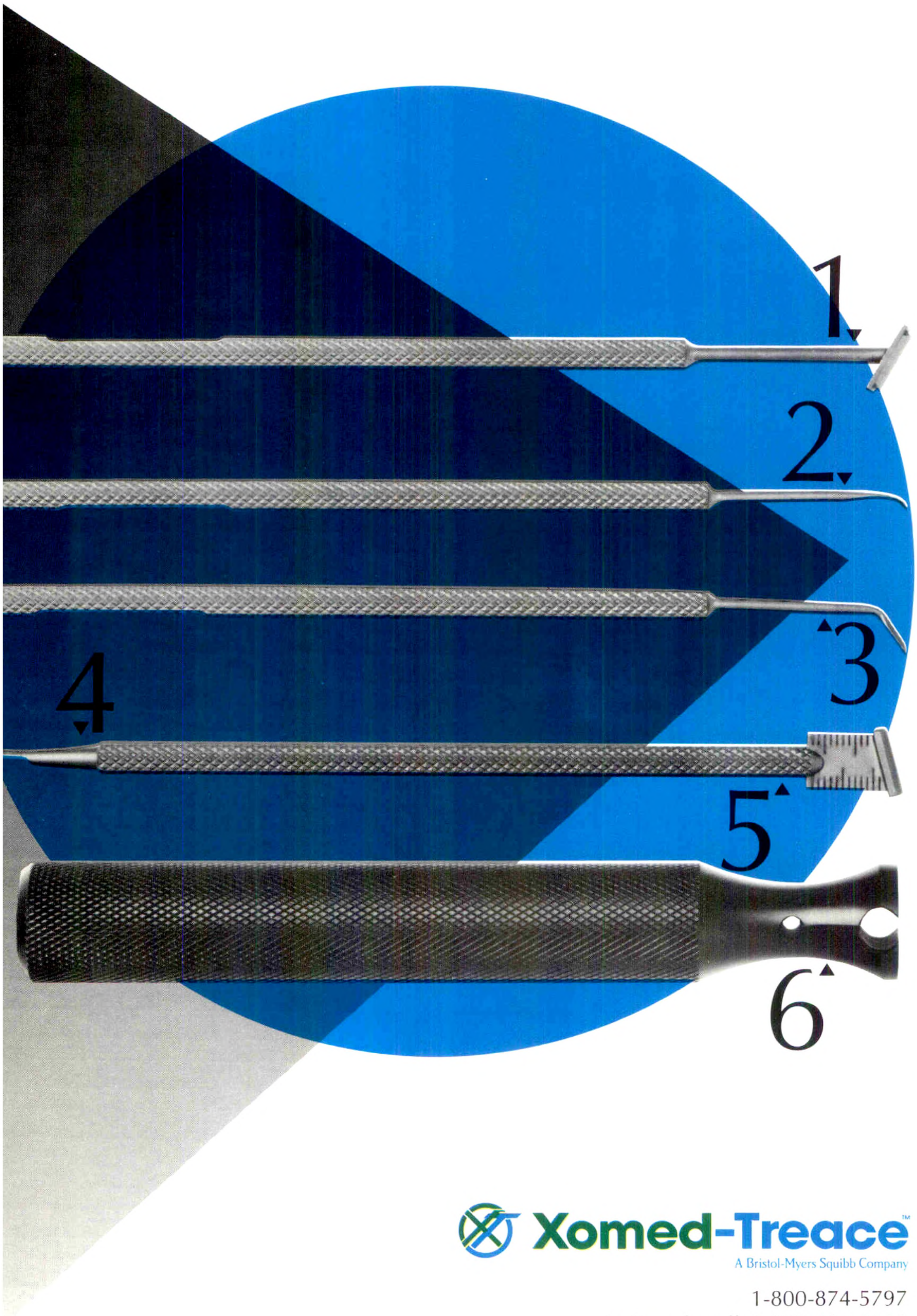

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DIFFICULTIES IN ENDOSCOPIC REMOVAL OF TEFLON GRANULOMAS OF THE VOCAL FOLD

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The difficulties in treating granulomas resulting from Teflon injection into the vocal fold are underreported in the literature. We have reviewed our experience with nine patients undergoing 27 procedures for Teflon granuloma. Two patients required tracheotomy before undergoing endoscopic granuloma removal because of airway compromise, and a third required urgent tracheotomy following endoscopy. One of the patients requiring elective tracheotomy had a granuloma that extended across the midline to the contralateral arytenoid, causing its fixation. Arytenoidectomy was required for decannulation in this patient. In all but one patient the granuloma nearly completely replaced the thyroarytenoid muscle. This extensive involvement often precludes the adequate excision of the granuloma in a single procedure; however, the microflap technique allows mucosal preservation to facilitate future procedures. In some cases the granuloma destroys large amounts of mucosa, and a microflap cannot be elevated and saved. The difficulties of excision are related to the near-total replacement of the thyroarytenoid muscle by granuloma. This paper will help the otolaryngologist–head and neck surgeon understand this destructive process and the resulting difficulties in surgical rehabilitation.

KEY WORDS — granuloma, larynx, laser, Teflon.

INTRODUCTION

Since its introduction in the mid-1960s, endoscopic injection of polytetrafluoroethylene (Teflon) has gained widespread use in the treatment of unilateral vocal fold paralysis. Teflon is injected lateral to the vocal process, between the inner perichondrium of the thyroid cartilage and the thyroarytenoid muscle, to move the paralyzed vocal fold toward the midline, providing a surface against which the mobile fold may vibrate. The procedure may help prevent aspiration as well as improve the voice. Early reviews of the procedure were quite favorable, describing Teflon as nonmigrating, noncarcinogenic, and having minimal foreign body reaction.[1] Some reviews quote a success rate in excess of 95% in treating vocal fold paralysis with Teflon injection.[2,3]

As experience with the procedure accumulated, its limitations were recognized and alternatives were proposed. While Teflon granuloma is recognized as a rare complication, it is often described as a simple problem remedied by complete excision in one or two procedures.[1,4,5] Our experience with Teflon granuloma shows that it is a far more formidable problem than the literature describes.

MATERIALS AND METHODS

The clinic and inpatient hospital charts of nine patients with Teflon granuloma were reviewed. Particular attention was paid to the number of Teflon injections received, the interval between the first Teflon injection and the initial presentation to us, details of the operative notes, the need for tracheotomy, the number of procedures performed, and whether or not an acceptable result had yet been achieved. We defined an acceptable result as 1) a voice usable for normal conversation, 2) no airway difficulty and successful decannulation if a tracheotomy had been required, and 3) no further procedures planned.

Preoperative evaluation included indirect laryngoscopy via a mirror or fiberoptic endoscope and videostrobolaryngoscopy. Computed tomography (CT) of the neck and/or plain tomograms of the larynx and trachea were performed in some cases.

Operative Technique. Direct laryngoscopy was performed in the operating room. General anesthesia was established and the patient was intubated with a laser-safe tube (LaserShield II, Xomed-Treace). Dexamethasone sodium phosphate 10 mg and cefazolin sodium 1 g were administered intravenously. Laser safety techniques, described elsewhere,[6] were also employed.

The initial examination was performed with a Holinger anterior commissure laryngoscope. Microlaryngoscopy was performed with either the Ossoff-Karlan modified Dedo laryngoscope or the Dedo photographic laryngoscope to achieve optimal exposure of the vocal folds.

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Presented at the meeting of the American Laryngological Association, Palm Desert, California, April 11-12, 1992.

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PATIENT SERIES SUMMARY OF TEFLON GRANULOMAS

Case No.	*Age*	*Sex*	*Side*	*Cause of Vocal Fold Paralysis*	*No. of Injections*	*Time From Injection to Presentation*	*Presenting Symptoms*	*No. of Endoscopic Procedures*	*Tracheotomy*	*Result*
1	70	F	R	Thyroidectomy	2	14 y	Lump in throat, shortness of breath, exercise intolerance	8	Yes	Acceptable
2	55	M	L	Thoracic aortic aneurysm	1	9 mo	Hoarseness, strained voice	1	No	Acceptable
3	43	F	L	Idiopathic	2	3 y	Hoarseness	2	No	Acceptable
4	60	F	L	Thyroidectomy	2	5 y	Shortness of breath, dyspnea, cough	7	Yes	Tracheotomy in place
5	59	F	R	Acoustic neuroma	1	2 y	Hoarseness, airway obstruction	2	No	Acceptable
6	71	M	L	Carotid endarterectomy	1	4 mo	Hoarseness	2	No	Persistent granuloma
7	62	F	R	Removal of neck neurilemoma	2	1.5 y	Dysphonia	1	Yes	Tracheotomy in place
8	58	F	L	Thyroid lobectomy	1	5.5 y	Throat pain with phonation	2	No	Improved
9	70	M	L	Excision of neck mass	1	?5-10 y	Hoarseness, pneumonia	2	No	Acceptable

The Teflon granuloma was examined with the operating microscope (2x to 10x) and palpated with a No. 5 microsuction. A preoperative photograph was taken with a 35-mm camera coupled to a 0° Hopkins rod telescope. An attempt was made to expose the granuloma via a microflap approach as previously described.[7,8] Special microinstruments designed for this procedure were used. An incision was made in the most lateral part of the superior surface of the vocal fold with either the sickle knife or the carbon dioxide (CO_2) laser (Sharplan 1060) delivered via a 0.25-mm microspot (Sharplan) to make a series of single-pulse burns (4 W, 0.1-second pulse) through the mucosa along the proposed incision. The incision was deepened to Reinke's space by means of up-cutting microscissors. The mucosal cover was elevated from the underlying granuloma from lateral to medial with flap elevators and microscissors. Granuloma tissue was ablated or excised with the laser in repeat mode, 4 to 8 W, 0.1-second pulse duration. Superpulse mode was used in one case in which the granuloma was particularly resistant to ablation. Oozing was controlled with neurosurgical pledgets moistened with 1:10,000 epinephrine hydrochloride or with a defocused laser.

Because the granuloma was often a poorly defined mass involving nearly all of the thyroarytenoid muscle, complete removal of the granuloma would require a complete cordectomy, resulting in an unacceptable voice and a risk of aspiration. The goal of excision, therefore, was to remove enough granuloma tissue to improve the airway but preserve enough tissue to provide a straight edge against which the contralateral vocal fold could vibrate. A wedge of granuloma tissue was removed or ablated from the most lateral portion of the vocal fold, and the remaining tissue was contoured to approximate as nearly as possible the shape of a normal vocal fold in the median position. Care was taken to work as far laterally as possible and avoid manipulation of the free edge of the vocal fold. The microflap was then returned to its original position. Photographs were taken, lidocaine hydrochloride (4%, 5 mL) was sprayed on the vocal folds to protect against laryngospasm, and the laryngoscope was removed.

Unless overnight observation for a questionable airway was indicated, the patient was discharged the same day following surgery. Ranitidine hydrochloride (150 mg twice a day for 30 days) and trimethoprim 80 mg, sulfamethoxazole 400 mg (twice a day for 10 days) were prescribed. Voice rest for up to 7 days was also used in some cases. The first follow-up visit was usually in 4 weeks, when indirect laryngoscopy and videostrobolaryngoscopy were repeated.

Nine patients with Teflon granuloma were referred to us 4 months to 14 years after their first Teflon injections (see Table). There were three men and six women ranging in age from 43 to 71 years. Causes of initial vocal fold paralysis included thyroidectomy or thyroid lobectomy, thoracic aortic aneurysm, carotid endarterectomy, excision of neck mass, and excision of acoustic neuroma. A patient with idiopathic vocal fold paralysis had spontaneous return of fold mobility following Teflon injection. Five patients had received a single Teflon injection, and four patients had received two injections. None of the patients in this study had their Teflon injection(s) performed at our institution.

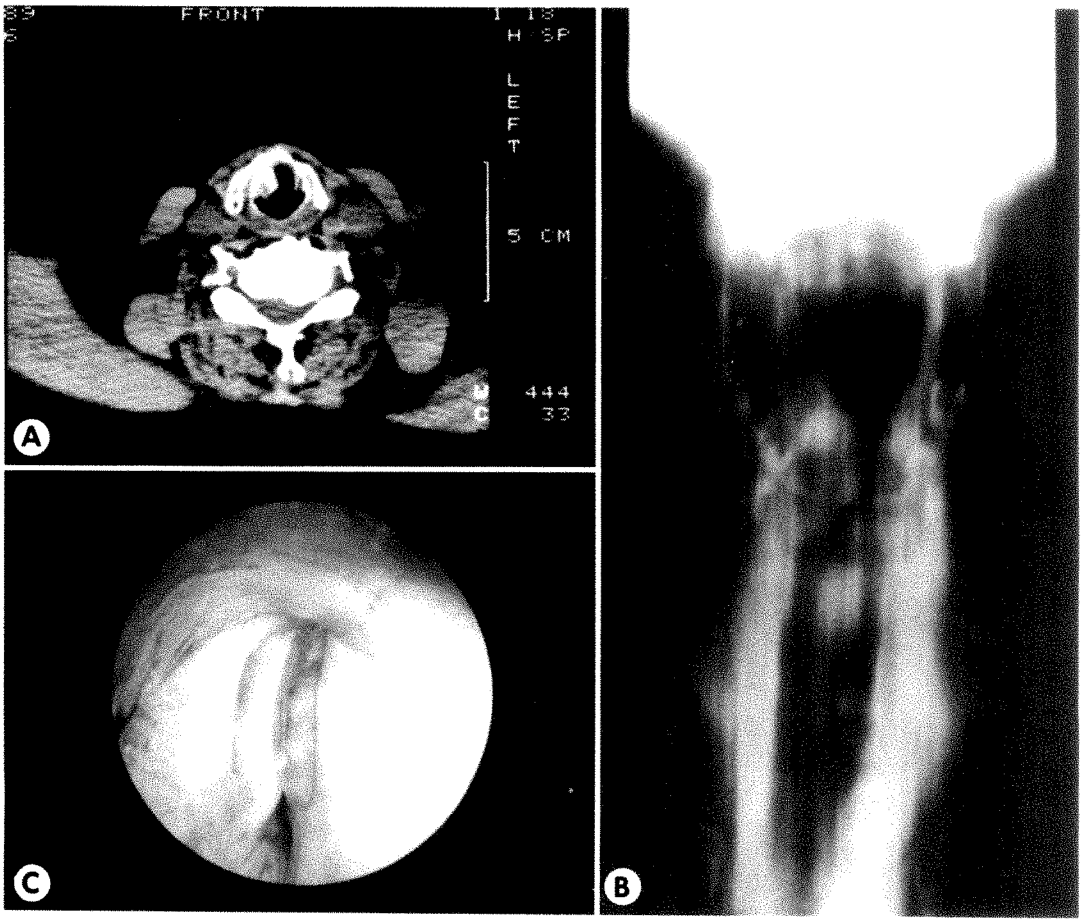

Fig 1. (Case 1) A) Computed tomogram showing right-sided subglottic mass. B) Tomogram showing right-sided glottic and subglottic mass and compromised airway. C) Microlaryngoscopy showing mass within right vocal fold. Vocal fold is erythematous and misshapen.

Three patients complained of shortness of breath or airway obstruction. Two patients reported throat pain or a sensation of a lump in the throat. Six patients complained of hoarseness or dysphonia with a strained voice.

Seven patients gave a history of immediate voice improvement after injection, followed by gradual deterioration of the voice over the next several months to years. Two patients simply reported no voice improvement following injection.

CASE REPORTS

The three cases selected demonstrate a severe case, a mild case, and a typical case of Teflon granuloma.

Case 1. A 70-year-old woman was referred in January 1989 after an emergency room visit for chronic shortness of breath that had been exacerbated by an upper respiratory tract infection. She had suffered right vocal fold paralysis following total thyroidectomy in 1974 for a goiter. Her right vocal fold was injected with Teflon in 1974 and again in 1975. She described progressive shortness of breath and exercise intolerance over the ensuing 14 years. Laryngoscopy revealed a large submucosal mass within the right true vocal fold. The left fold appeared normal and was mobile. A CT scan (Fig 1A) and a plain tomogram (Fig 1B) showed a mass within the right glottis and subglottis with airway compromise.

She was taken to the operating room, where local tracheotomy was performed. Microlaryngoscopy showed a firm, immobile mass with a large subglottic component (Fig 1C). The mass was partially excised with the CO_2 laser. The microflap technique was used to preserve the mucosal cover. Because the granuloma had diffusely infiltrated the vocalis muscle, dissection was difficult. Histologic examination of the excised material revealed foreign material with a foreign body reaction consistent with the diagnosis of Teflon granuloma.

She was returned to the operating room in March 1989. The right vocal fold mass was slightly reduced in size, but retained a persistent subglottic component. An endoscopic right partial cordectomy was performed with the CO_2 laser. No microflap was used.

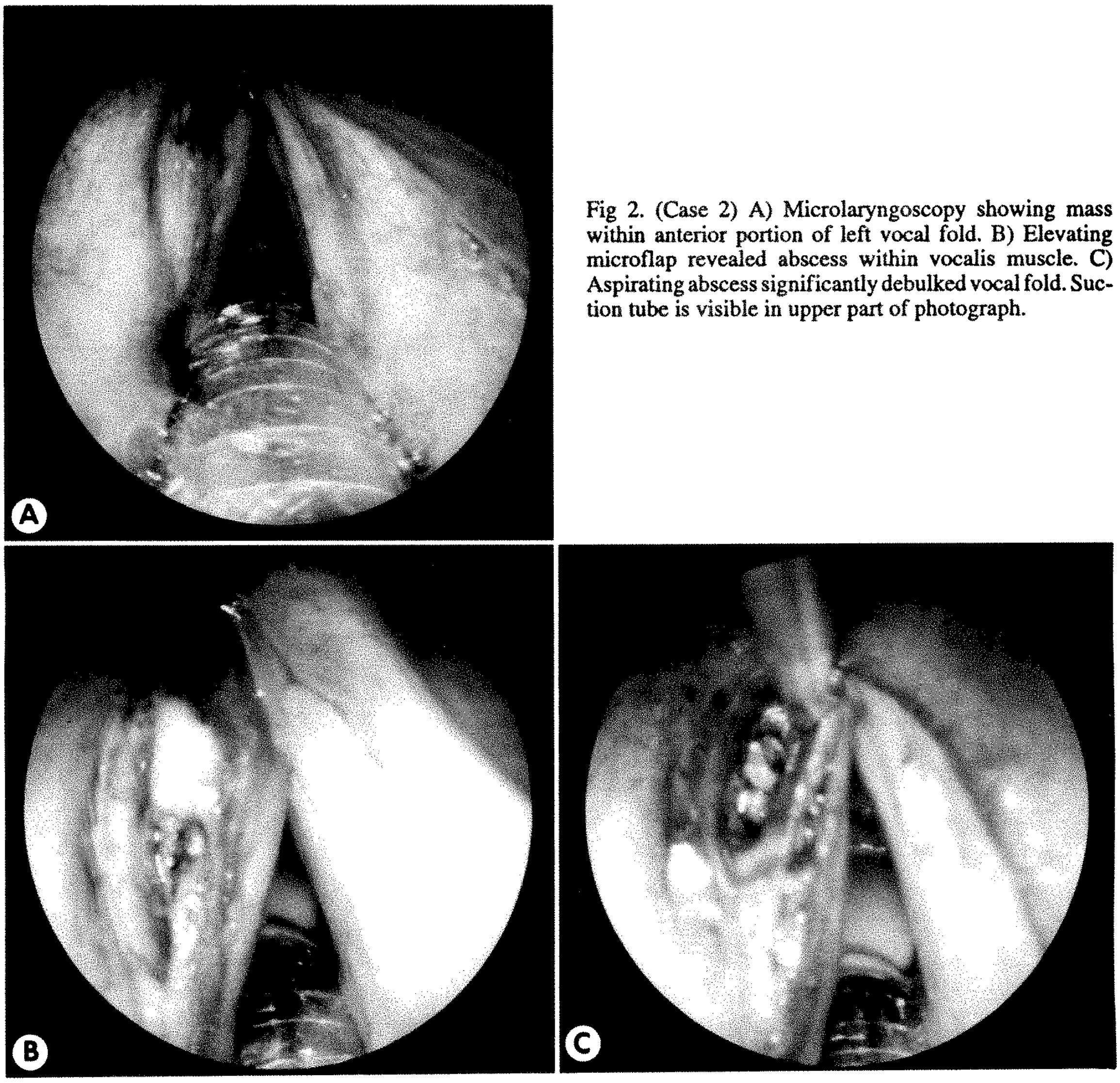

Fig 2. (Case 2) A) Microlaryngoscopy showing mass within anterior portion of left vocal fold. B) Elevating microflap revealed abscess within vocalis muscle. C) Aspirating abscess significantly debulked vocal fold. Suction tube is visible in upper part of photograph.

In April and again in June 1989 she was examined in the operating room and found to have persistent granuloma in the right vocal fold, as well as some granulation tissue in the trachea above the tracheotomy tube. On both occasions the granuloma was debulked further and the granulation tissue within the trachea was removed with the CO2 laser. Her glottic airway remained inadequate.

Over the next 6 months no further procedures were performed. The granuloma had reduced to 50% of its original size. However, we noted at this time that the left vocal fold had decreased mobility. By January 1990 the left vocal fold was nearly completely immobile. The right fold continued to decrease in size; only some residual granuloma remained within the ventricle. The airway was still too small to consider decannulation.

The following month a right endoscopic laser arytenoidectomy and partial cordectomy was performed. The procedure was revised in May. Recurrent granulation tissue within the trachea above the tracheotomy site was also removed.

Her last procedure was in June 1990. The right vocal fold was debulked further, and persistent suprastomal granulation tissue was again removed. Her tracheotomy tube was plugged following surgery, and she was decannulated the following day. Her voice and airway have been acceptable since that time.

Case 2. A 55-year-old man developed paralysis of the left vocal fold from a thoracic aortic aneurysm. The paralysis persisted after the aneurysm was repaired in October 1988. A Teflon injection in June 1989 improved his voice initially, but he gradually became hoarse and had to "strain" to speak.

He was referred in December 1989. Videolaryngoscopy showed a paralyzed, erythematous left vocal fold that was bowed medially in its anterior third.

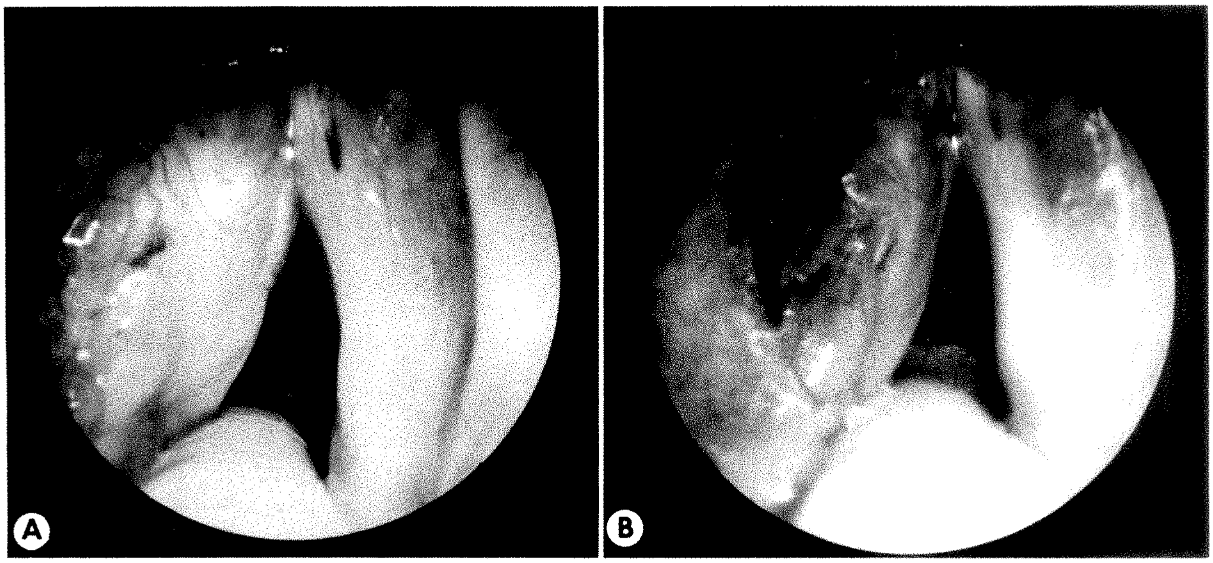

Fig 3. (Case 3) A) At patient's second microlaryngoscopy, left vocal fold mass persisted. B) Granuloma was again debulked via microflap approach and carbon dioxide laser. Laser ablation of Teflon left behind thick, black char.

During phonation posterior glottic incompetence was seen. Stroboscopy showed a normal mucosal wave over the right vocal fold. The mucosal wave on the left was absent.

He was taken to the operating room for microlaryngoscopy and debulking of the granuloma via a microflap approach. The granuloma occupied the anterior and middle thirds of the vocal fold (Fig 2A). When the microflap was elevated, an abscess and a cavity filled with serosanguinous fluid were found within the vocalis muscle (Fig 2B). Aspiration of these and excision of the granuloma significantly debulked the left vocal fold (Fig 2C). Follow-up 1 month later revealed a markedly improved voice and improved posterior glottic closure.

Case 3. A 43-year-old woman employed as a teacher developed hoarseness and a left vocal fold paralysis for which no cause was found. Two Teflon injections restored a usable voice, but over the next 3 years her voice deteriorated. During this time her left vocal fold spontaneously regained movement. Removal of Teflon from the vocal fold was attempted by the referring physician, but her voice did not improve following this procedure.

On her referral visit in July 1990, she complained of hoarseness that often progressed to complete loss of voice. Her ability to teach was severely impaired. Laryngoscopy via a flexible endoscope showed a large submucosal infraglottic mass in the left vocal fold. Videostroboscopy showed an absent mucosal wave on the left and a weak, aperiodic mucosal wave on the right.

She went to the operating room for microlaryngoscopy and debulking of the left vocal fold by the CO_2 laser and the microflap approach. Examination under high magnification showed a dehiscence in the infraglottic mucosa where the granuloma had penetrated it from beneath. The microflap was elevated in the subglottic area with great difficulty. Frequent bleeding was controlled with adrenalin-soaked cottonoids. Necrotic vocalis muscle was debrided.

Follow-up at 1 month and 4 months postoperatively showed some voice improvement. Examinations showed persistence of the left infraglottic mass. Videostroboscopy showed an improved mucosal wave on the right side. She was returned to the operating room for microlaryngoscopy and further debulking of the granuloma (Fig 3). At 3-month follow-up her voice was still rough, but speaking required much less effort. She was able to teach the following semester.

RESULTS

These nine patients have undergone one to eight endoscopic procedures each, for a total of 27 endoscopic procedures. Review of the operative notes reveals similarities regarding the descriptions of the granulomas and the difficulties encountered in removing them. The granulomas are described as rock-hard masses involving almost the entire vocal fold. They often have penetrated and destroyed the overlying mucosa from beneath, making the microflap difficult to elevate. There is also frequently a large infraglottic component that is difficult to reach endoscopically. Debulking the granulomas with the CO_2 laser proceeds slowly, with frequent interruptions for hemostasis using adrenalin-soaked cottonoids, defocused laser, or both.

Three patients required tracheotomy. In two patients tracheotomy was performed electively before the first endoscopic procedure. The third tracheotomy was urgently performed for shortness of breath and stridor on the evening following the patient's first endoscopic procedure. A fourth patient was urgently returned to the operating room on the evening following surgery for additional vocal fold debulking because of airway compromise.

To date five patients have achieved an "acceptable" result as previously defined. In four of these five patients there is a direct relationship between the amount of time from the first Teflon injection to presentation and the number of procedures required to achieve an acceptable result. One patient (case 2), presenting 9 months after injection, had an acceptable result from a single procedure. Two patients (cases 3 and 5), presenting 2 to 3 years after injection, required two procedures. The fourth patient (case 1), injected 14 years prior to presentation, required eight procedures, including tracheotomy. Arytenoidectomy and partial cordectomy were then required for decannulation. Among the four patients who have not yet achieved an acceptable result, one (case 4) was injected 5 years before presentation and has to date undergone seven endoscopic procedures.

DISCUSSION

Although Teflon injection for unilateral vocal fold paralysis has gained widespread popularity, the limitations of the procedure have been recognized in recent years. The worst of these include the irreversible nature of the procedure, the low margin for error in the location and quantity of the injection,[9] the risk of Teflon migration and/or granuloma formation,[10] and the risk of spontaneous return of fold movement following injection.[4,9,11] Other shortcomings include the nonphysiologic mass, tension, and vibratory properties of the injected fold[9,10] and the need for awake laryngoscopy.[12] A number of alternatives have been proposed, including ansa hypoglossi to recurrent nerve anastomosis,[10] fold injection with fat[13] or collagen,[12] nerve-muscle pedicle transfer,[14] and type I thyroplasty–Silastic block medialization of the paralyzed fold.[11]

Granuloma formation following Teflon injection is rare. It has a reported incidence of less than 1%.[1,5] Reports of removal of Teflon granuloma describe good results, often with a single procedure. The granuloma is removed through an opening in the superior aspect of the true fold[5] or the false fold.[15]

Horn and Dedo[5] described a series of 12 Teflon-injected patients with convex vocal folds and hoarseness. Of these 12, 1 was reported to have a granuloma. Ten were debulked via a superior cordotomy approach. Only 4 of these 10 were adequately treated with a single procedure. The remainder required up to three procedures. Seven patients had a "good to excellent" voice result. No airway difficulties were described, and none of the patients required tracheotomy.[5]

Patients in our series, however, had both airway and voice difficulties and required up to eight endoscopic procedures each. Three patients required tracheotomy to secure a safe airway. Using subjective criteria (see Materials and Methods), we have found that only five of the nine patients have an acceptable voice and airway. We acknowledge, however, that our series suffers from the selection bias inherent in a tertiary referral laryngology practice. We also acknowledge that both the "acceptable result" criteria and the data to which they are applied are subjective. Our evaluations would be improved by including more objective tests such as flow volume loops and airflow rate during phonation.

Surgical Technique. In vivo ablation of Teflon granuloma by the CO_2 laser has been described. Because of the fear of Teflon ignition from laser impact, use of the laser has been limited to the mucosal incision only.[15] We have tried granuloma removal using conventional techniques and have encountered unacceptable bleeding. Furthermore, the risk of laser impact igniting a mature granuloma is small.[15] We therefore use the CO_2 laser in the repeat-pulse mode for granuloma removal. Tissue is ablated with a focused 0.25-mm microspot, and bleeding is controlled with a defocused spot and neurosurgical pledgets moistened with 1:10,000 epinephrine. While bleeding still occurs during laser removal, it is less frequent and more easily controlled.

In our series of nine patients we have encountered surgical difficulties not described in the literature. Debulking the granuloma is a slow, arduous process requiring up to 2 hours of laser use. Despite the use of the laser, bleeding is frequent. Ablated Teflon leaves behind a thick, tenacious char. The mucosa is often dehiscent over the granuloma, and the granuloma often has a significant subglottic component. The microflap used to gain access to the granuloma is therefore not always preserved completely intact. However, because the mucosal cover is at least partially preserved, scarring is reduced, and future procedures are made easier.

Many of these difficulties are related to the physical properties of Teflon. Polytetrafluoroethylene (Teflon) is a heat-stable compound with an absorbance peak between 800 and 900 nm,[16] well away from the 10,600-nm wavelength of the CO2 laser. Teflon is extremely heat-stable, requiring temperatures in excess of 500°C for thermal decomposition.[17] This thermal stability allows much higher temperatures to be reached during laser impact than in normal tissue, which quickly vaporizes on reaching 100°C. Ablation of Teflon with the CO2 laser may therefore cause thermal damage to the surrounding tissues. We believe, however, that the 0.25-mm microspot minimizes thermal damage and makes use of the CO2 laser practical in this setting.

Tissue Response to Teflon. The tissue reaction following Teflon injection is a classic foreign body response and probably occurs following all Teflon injections. Teflon paste is a 50-50 mixture of Teflon and glycerin. Teflon particles in the paste range in size from 50 to 100 µm.[18] Within 48 hours after injection an acute inflammatory response occurs that is characterized by polymorphonuclear leukocytes and edema.[19] Larynges examined 4 weeks following injection show mononuclear cells accumulated at the edge of the Teflon mass. At 3 months, strands of fibrous tissue have infiltrated the Teflon.[18] By 6 months postinjection this is replaced by a typical foreign body reaction consisting of dense collagenous tissue and giant cells containing glassy, birefringent material. This material is identified as Teflon by its characteristic infrared absorbance and x-ray energy dispersion patterns.[16] Granulomas over 10 years old contain Teflon granules as small as a few microns in diameter.[18] The reaction is very infiltrative and usually involves much of the thyroarytenoid muscle. As stated by Rubin,[20] excising a granuloma without removing most of the thyroarytenoid muscle is difficult.

This literature review suggests that Teflon granulomas reach histologic maturity approximately 6 months after fold injection. It is interesting, then, that some patients in this series developed symptoms over several years following a period of voice improvement immediately after injection. We have also observed a direct relationship between the interval from Teflon injection to initial presentation and the number of procedures required to achieve an acceptable result. In other words, older granulomas seem to be more severe and more difficult to treat. This suggests that a Teflon granuloma may continue to proliferate in a slow but unpredictable manner long after it is histologically mature. The granuloma grows as long as there is extracellular Teflon to stimulate giant cell activity and proliferation. If the granuloma ever becomes large enough or invades a critical area (ie, infraglottic area, vocalis muscle, or anterior vocal fold), symptoms of hoarseness, strained voice, or airway compromise develop.

It is also possible that surgical manipulation of the granuloma might further stimulate its proliferation. This might explain why these granulomas persist even after multiple attempts at excision. The first case presented (case 1) is particularly interesting in this regard. After four endoscopic procedures for granuloma limited to the right vocal fold, the process appeared to spread to the left arytenoid, causing its fixation. We believe that surgical manipulation may have stimulated further granuloma formation and invasion of the contralateral larynx. It is possible, however, that scarring and inflammation from multiple endoscopies and excisions may have been responsible. Biopsy of the posterior cricoarytenoid muscle or contralateral cricoarytenoid joint would probably help answer this question, but carries the risk of further injury in a critical area of the larynx.

CONCLUSION

Teflon granuloma of the vocal fold is a rare complication of Teflon injection. Endoscopic excision by CO2 laser of these granulomas presents surgical difficulties not previously described. Laser ablation of granuloma is a slow process resulting in thermal damage to surrounding tissue. Several procedures are often required to achieve an acceptable airway and voice. Tracheotomy is sometimes required to ensure a safe airway until granuloma is adequately excised. Furthermore, the process of surgical manipulation and excision may stimulate further growth of the granuloma. This study helps the otolaryngologist–head and neck surgeon understand this destructive process and the challenges in surgical rehabilitation.

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4TH INTERNATIONAL ACADEMIC CONFERENCE IMMUNOBIOLOGY IN OTOLOGY, RHINOLOGY AND LARYNGOLOGY

The 4th international academic conference Immunobiology in Otology, Rhinology and Laryngology will be held in Oita, Japan, April 4-7, 1994. For further information contact Goro Mogi, MD, Dept of Otolaryngology, Oita Medical University, Hasama-machi, Oita 879-55, Japan; telephone 81-975-49-4411 ext 2912 or 2913; fax 81-975-49-0762.

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SILASTIC MEDIALIZATION AND ARYTENOID ADDUCTION: THE VANDERBILT EXPERIENCE

A REVIEW OF 116 PHONOSURGICAL PROCEDURES

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From April 1987 to April 1992, 116 phonosurgical procedures were performed to treat glottal incompetence. The initial numbers of these surgical procedures included the following: 29 primary Silastic medializations, 3 primary Silastic medializations with arytenoid adduction, 53 secondary Silastic medializations, 4 secondary Silastic medializations with arytenoid adduction, and 11 bilateral Silastic medializations. These procedures are useful in treating unilateral true vocal cord paralysis, scarring, bowing, or paresis, as well as bilateral true vocal cord bowing. Of the initial 100 patients, 16 later underwent a revision with either a larger implant's being placed or an arytenoid adduction. Primary Silastic medialization is the placement of an implant under general anesthesia in the same surgical setting in which laryngeal innervation is sacrificed. Secondary Silastic medialization is the placement of an implant under local anesthesia for a preexistent vocal cord malfunction. In either case, overall voice results for unilateral paralysis are very good. Primary Silastic medialization significantly decreases the postoperative rehabilitation period in skull base patients because of the immediate postoperative glottal competence and decreased use of perioperative tracheotomy. Bilateral implants yielded good results in 6 patients with presbylaryngis, but 6 other patients with bowing from other causes experienced only moderate improvement in speech quality. There were no implant extrusions; however, 1 implant was removed secondary to a persistent laryngocutaneous fistula in a patient who had previously undergone laryngeal irradiation. This was the only complication in this series.

KEY WORDS — arytenoid adduction, glottis, medialization, phonosurgery, Silastic, thyroplasty, vocal cord.

INTRODUCTION

Silastic medialization (SM; thyroplasty type I) and arytenoid adduction (AA) have provided significant improvement to the care of patients with glottal insufficiency due to paralysis, paresis, scarring, or bowing of the true vocal cords (TVCs). Two review articles on this subject by Koufman[1] and Koufman and Isaacson[2] provide an excellent historical background. Although several series had been previously reported, medialization did not receive significant attention as a treatment for vocal cord paralysis until Isshiki et al[3,4] advanced the technique using Silastic as the implant. Isshiki deserves credit as the author of the surgical procedure most used today. Koufman[5] helped to popularize the procedure within the United States, as well as adding further refinements to the surgical techniques. Series by Maves et al[6] and Tucker[7] supported the high-quality results provided by the procedure, yet pointed out its limitations and potential complications. The purpose of this paper is to review the results of our series derived over the last 5 years and discuss further refinements in surgical technique and instrumentation. By drawing on otologic surgical techniques, we developed a less traumatic and more accurate procedure for implant placement. The patients will be divided into different procedure categories for more accurate comparison and assessment.

PATIENT EVALUATION AND SURGICAL TECHNIQUE

From April 1987 to April 1992, 116 procedures for glottal incompetence were performed at our institution. These procedures included primary SM (performed under general anesthesia at the time of neural sacrifice), secondary SM (performed under local anesthesia), bilateral SM, and AA. Recently, ansa–recurrent laryngeal nerve (RLN) transfer has been combined with SM when indicated. The surgical techniques we use for both SM and AA are modifications of the original descriptions of Isshiki et al.[3,4,8] Although we have outlined our surgical techniques before, we would like to amplify these to demonstrate the significant changes that have evolved over the last 3 years.[9]

Patients presenting with preoperative voice deficiency received an extensive evaluation, which included a complete head, neck, and chest examination. Patients who present with idiopathic paralysis undergo a magnetic resonance imaging scan to evaluate the entire course of the ipsilateral vagus nerve. If an abnormality is suspected at the level of the skull base,

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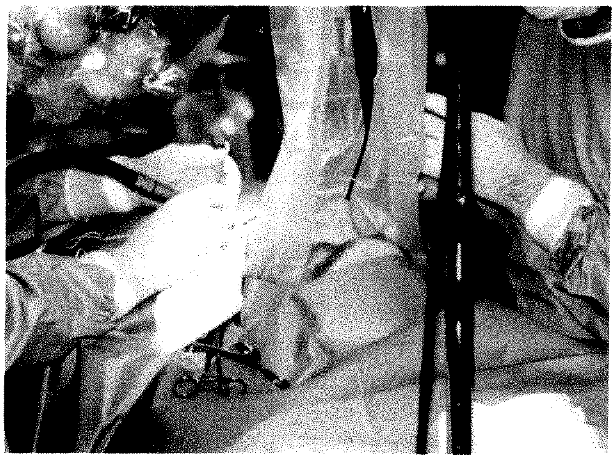

Fig 1. Flexible nasopharyngoscope is attached to intravenous pole for support and sterilely draped so surgeon can manipulate it during procedure to maintain best view of true vocal cords.

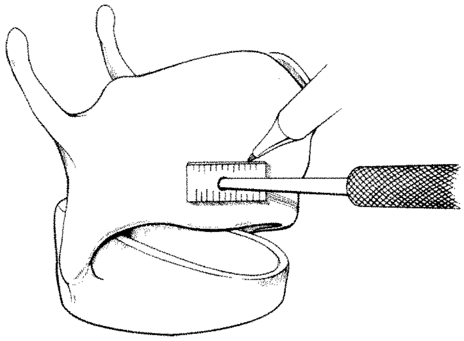

Fig 2. Window is positioned parallel to lower border of thyroid cartilage. Window template is helpful in laying out this window; it is placed 5 to 8 mm back from prow of larynx and 3 mm up from inferior border.

a computed tomography scan is used for higher resolution of the bone–soft tissue interface. Laryngeal function tests, videostroboscopic evaluation, and voice analysis are also performed. The composition of this evaluation has matured as our series has progressed. Many of the early patients did not undergo laryngeal function tests or voice analysis. Although the human ear remains the most accurate judge of improvement in voice quality, it is quite difficult to objectively quantify this improvement for presentation. Therefore, over the last 2 years we have tried to identify which objective tests in the laryngeal function and voice analysis battery best correlate with improvement in voice quality.

The preoperative videostroboscopy demonstrates the position of the paralyzed TVC. If during phonation the mobile vocal process comes into contact with the paralyzed vocal process, then usually SM alone results in marked improvement. If there is a wide posterior glottic gap with the vocal processes widely spaced, then the patient is prepared for SM with the possible addition of AA.

Silastic medialization (either unilateral or bilateral), ansa-RLN transfer, and AA are all performed with local anesthesia, supplemented by intravenous sedation. Patients are monitored by the anesthesiology service throughout the procedure. It is not necessary for the success of the procedure to use transnasal flexible videolaryngoscopy. The size of the laryngeal implant, or the degree of adduction, is mainly dependent on the quality change in the voice obtained during the procedure. We, however, continue to use intraoperative laryngeal video monitoring on all local procedures (Fig 1). It provides excellent feedback to demonstrate the position of the TVC in relation to the window created in the thyroid cartilage, and helps to prevent overmedialization of the false vocal cord (FVC) or the ventricle. It is particularly helpful during AA to prevent overadduction of the vocal process. The same feedback can be obtained by intermittent observation of the larynx with the nasopharyngoscope by either the surgeon or an assistant. If video monitoring is used, the patient should receive atropine and topical nasal anesthesia preoperatively to decrease excess pharyngeal secretions that would block the view of the nasopharyngoscope.

The larynx is exposed through a small incision overlying the midportion of the thyroid cartilage, and the perichondrium is elevated from the involved side. The window template, which is 6 x 13 mm, is positioned over the cartilage to mark the window location (Fig 2). The window is placed parallel to the lower border of the thyroid cartilage. The plane forming the lower border of the thyroid cartilage is formed between the anterior lower edge and the portion behind the muscular process. The inferior extension of the muscular process at the anterior third of the lower border of the thyroid cartilage is quite variable.

If the plane between the anterior point of the thyroid cartilage and the maximum inferior extension of the muscular process is used as the parallel line for the lower border, the window may be tilted too far inferiorly at its posterior point. The window should be placed as close to the lower border of the laryngeal cartilage as possible, while leaving a strong inferior cartilage strut to resist fracture while placing the implant. The distance from the anterior commissure back to the anterior edge of the window is determined by the shape of the cartilage. In the more obtuse-angled cartilage, as seen more often in women, the window is placed closer to the prow of the larynx (Fig 3A). When the laryngeal angle is more acute, as seen most often in men, the window is moved more posterior to prevent overmedialization of the anterior third of the cord. When calcified, the cartilage is removed from the outlined window under magnification, by means of an otologic drill with a 2- to 3-mm cutting bur (Fig 4A). The internal perichondrium is left intact at this point. In the younger patient, with little or no calcification of the cartilage, a sharp elevator can be used to remove this cartilage island.

By removing all of the cartilage from the window,

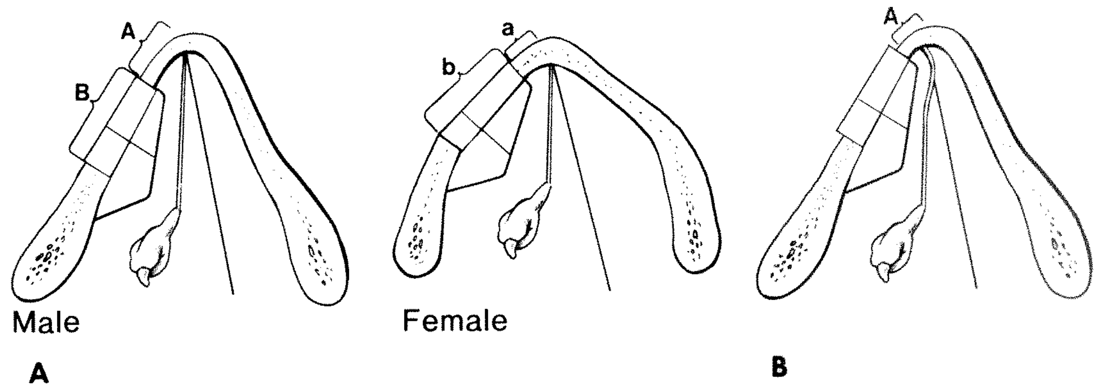

Fig 3. A) Although either laryngeal shape can be seen in either sex, women usually have more obtuse anterior angle, and men more acute anterior angle, of thyroid cartilage. Average window setback from anterior commissure is 7 mm in men (A) and 5 mm in women (a). This will prevent overmedialization of anterior commissure. Length of window (B,b) is same, 13 mm, in both men and women. B) Overmedialization of anterior commissure results in strained voice, even if posterior commissure is wide open. This can occur when window is placed too close to anterior commissure (A), or when too-large implant is placed.

greater accuracy in medialization can be achieved. The cartilage island, if left in place during medialization, can shift when the inverted Silastic T is positioned. If the island shifts superiorly, as we have seen in 1 patient referred to us for revision, then the FVC is medialized, resulting in poor vocal quality. If the island is pushed straight in, often the medialization is still too high, and ventricular mucosal prolapse occurs. If the cartilage island shifts inferiorly when the implant is placed, then good voice quality can occur; however, care must be taken to prevent overmedialization of the anterior TVC, which results in a strained vocal quality. Histologic evidence of this is seen in a recent case report by Isaacson et al.[10] One month after SM was performed, with an inverted Silastic T used to medialize the cartilage island, the patient died. Whole organ sectioning of the larynx demonstrated the overcompensation of the anterior half of the vocal cord by the cartilage island.[10] Because of this we prefer to remove the entire cartilage island. This allows the shaped implant to control more accurately the degree of medialization.

The short laryngeal elevator is used to begin elevation of the perichondrium from the inner surface of the thyroid cartilage. The inner edge of the cartilage window is smoothed with a small bur or an otologic curette. In several previous discussions of this procedure, the integrity of the inner perichondrium has been stressed, implying that injury to it would increase the likelihood of graft extrusion.[1,4,7] However, the operative techniques recommended in those same reports for creating the cartilage island included the use of the oscillating saw or a sharp surgical knife. We were fearful that these methods would not only injure the inner perichondrium, but would also cut through the thyroarytenoid fascia and the underlying distal branches of the superior laryngeal vessels.

There is a likelihood of opening into the laryngeal ventricle with these techniques, as well. To firmly establish this principle, we performed the first 40 procedures with an operating microscope, carefully removing the cartilage and leaving the inner perichondrium intact. The inner perichondrium was then widely elevated, and medialization was attempted. Rarely could adequate medialization be accomplished. Because of this finding, we microscopically incise the perichondrium with a small knife at the superior, posterior, and inferior margins of the window, making it a flap. The thyroarytenoid fascia and its underlying vessels are maintained intact. The long laryngeal elevator is then used to separate the thyroarytenoid muscle fascia from the inner perichondrium (Fig 4B). The distal superior laryngeal vessel branches can be seen lying under this fascia. At this point very accurate medialization can be accomplished. We feel the main reason for delayed graft extrusion into the larynx is injury to the laryngeal ventricle with implant contamination. For this reason we feel it is risky to use a paramedian incision adjacent to the anterior commissure for implant placement rather than using a window. The ventricle, which is adjacent to the inner perichondrium at the anterior commissure, can easily be injured with any paramedian cartilage incision. Several papers that have outlined this approach in the past have reported implant extrusions secondary to implant contamination.[1,11]

Even with the perichondrium sectioned, a capsule is formed around the implant, further preventing its extrusion (Fig 5). Using this technique we have had no extrusion of implants thus far. After the thyroarytenoid muscle elevation has been completed, the depth gauge (Fig 6) is employed. While viewing the larynx on the monitor, one can use the small end of the gauge to discretely medialize the tissue in the anterior, middle, and posterior aspects of the window. This is performed at the superior and inferior edges of the window in each of these positions, the resultant information showing the relationship of the window to the TVCs and FVCs. Usually, medialization at the superior aspect of the window results in movement of

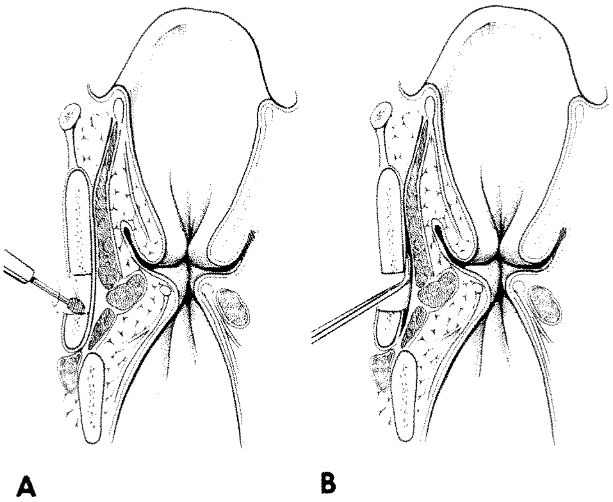

Fig 4. A) Under magnification, 2- to 3-mm cutting bur is used to remove cartilage from window. This can be done without injury to inner perichondrium. B) After perichondrium has been carefully incised along superior, posterior, and inferior margins of window, long laryngeal elevator is used to separate thyroarytenoid fascia away from inner perichondrium.

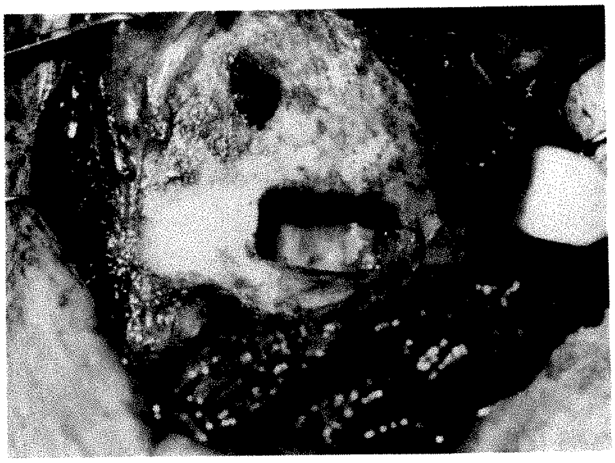

Fig 5. This view through thyroid cartilage window during revision operation in which larger implant was placed demonstrates fibrous capsule that develops around implant after placement.

the FVC and ventricular mucosa. For this reason, the implant is carved so that the plane of maximum medialization is at the lower edge of the window. The larger, sloped end of the depth gauge is then used to medialize the cord while the patient is phonating. The gauge can be moved or angled in any position to define the depths of the anterior and posterior aspects of the implant needed to acquire the best voice. These measurements are read off the gauge from the inner aspect of the thyroid cartilage. If the inner edge cannot be seen well, then the distance to the outer edge is recorded. The smaller end of the gauge can then be used to measure the anterior and posterior widths of the cartilage, which are subtracted from the measurements just acquired. Care must be taken to prevent overmedialization of the anterior third of the TVC, which results in a strained, spastic voice (Fig 3B).

After the implant dimensions have been acquired, the final implant is carved. We hope that a precarved implant will soon be released that requires only minor modifications for each patient's needs. Until then we continue to carve implants from Silastic block (Fig 7). Several implants are partially carved ahead of time to prevent lengthy carving during surgery.

Because of the shorter female vocal cord, the distance from the anterior aspect of the window to the maximum point of medialization is less in women. This, combined with the more obtuse shape of the female thyroid cartilage, results in an implant that is more equilateral in its two laryngeal surfaces. From the anterior edge of the implant to the maximum point of medialization is approximately 10 mm in women and 13 to 14 mm in men. If no return of vocal cord function is possible, then a 5- to 6-mm tail extends medially to the thyroid cartilage and posteriorly to the window. This extension of the implant is tapered to prevent contact with the muscular process of the arytenoid. Contact on the anterior surface of that process would prevent adduction of the process, working contrary to its proposed mechanism. If there is still a possibility of functional return of the vocal cord or the implant is being placed deep to a mobile cord because of paresis, scarring, or bowing, then the posterior extension may be decreased to ensure no interference with arytenoid movement.

To standardize our records we use the formula a x b x c...d to document the size in millimeters of the implants placed; "a" stands for anterior medialization, "b" for posterior maximal medialization, "c" for the overall length, and "d" for the length from the front of the implant back to the point of maximal medialization. A typical implant placed in a male larynx would be 2 x 6 x 18...13 mm. The implant is often divided into two pieces to allow a more gentle insertion (Fig 8A).

After the lower edge is placed into the window, the implant is rotated into position (Fig 8B). The posterior portion is placed first and moved back partially posterior to the window, after which the anterior half then locks the posterior segment in place. If the quality of the voice is not as good as expected, then the implant can be removed with two small skin hooks and adjusted appropriately. The time from intralaryngeal elevation to final placement of the implant needs to be as short as possible to allow for voice evaluation without the interference of edema. The final shape of the implant usually provides the maximum plane of medialization at the lower border of the window to prevent medialization of the FVC or the ventricular mucosa (Fig 9).

If it is obvious at this point that the posterior glottis cannot be closed, then an AA is performed. We perform this in a very similar manner to the original

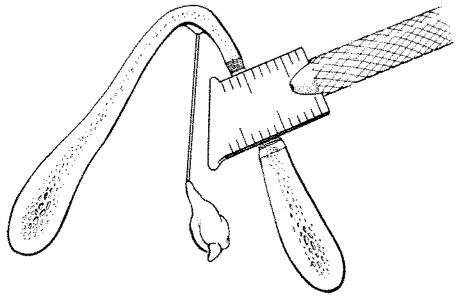

Fig 6. Depth gauge is very helpful in simulating medialization needed at both anterior and posterior aspects of vocal cord. It is thin enough to move up and down within window to identify level that will move true cord into position without medialization of false cord. Millimeter markings on gauge dictate anterior and posterior dimensions of implant.

description of Isshiki et al.[8] The posterior border of the thyroid cartilage can be approached by either dissecting lateral to the strap muscles and cutting through the inferior constrictor to expose the cartilage, or continuing the elevation of the outer perichondrium until the entire ala of the thyroid cartilage can be seen.

After the lateral edge of the thyroid cartilage is isolated, either the cricothyroid joint is opened for better access, or a portion of the posterior rim of the thyroid cartilage is removed to expose the muscular process of the arytenoid. The pyriform mucosa is carefully elevated until the posterior aspect of the arytenoid can be palpated. The posterior cricoarytenoid muscle can be removed from the muscular process of the arytenoid as needed for mobility of the cartilage. We rarely open the cricoarytenoid joint capsule as described by Isshiki et al.[8] This can lead to prolapse of the arytenoid cartilage into the laryngeal lumen with overadduction of the posterior commissure. A 3-0 Prolene suture is passed twice through the muscular process and the surrounding tissue and brought forward to reproduce the pull of the thyroarytenoid muscle on the muscular process. Arytenoid adduction is most often performed in conjunction with, or delayed after, SM; thus, the suture is passed through the paraglottic space and the Silastic implant. Only a gentle pull is necessary to adduct the vocal process. We move the arytenoid back and forth until the correct position is identified. The suture is tied over either the anterior portion of the implant or the lower border of the thyroid cartilage, about 5 to 8 mm back from the prow of the larynx.

If indicated after completion of SM, reinnervation as described by Crumley[12] is performed to suture a branch of the ansa-hypoglossal-cervicalis system to the cut end of the RLN. This, along with SM and AA, can easily be performed under local monitored anesthesia with intravenous sedation. The goal of this procedure is not the return of normal function, which is highly unlikely, but to maintain muscle bulk and provide static muscle tone within the laryngeal muscles. Many injuries to the RLN or the vagus nerve that produce TVC paralysis are the result of stretch or crush injuries with a high likelihood of delayed reinnervation. Often this regrowth does not result in physiologic motion of the cord, but activity on electromyography (EMG) confirms the reinnervation. This regrowth will maintain the muscle bulk and provide tone, making nerve transfer unnecessary. If division of the RLN or vagus nerve is known to have occurred within 2 years of the potential date of repair, then reinnervation is indicated if no spontaneous regrowth has occurred.

This determination is confirmed with either preoperative or intraoperative EMG. If normal EMG activity is absent and no reinnervation potentials are seen, then nerve transfer is performed along with SM. If neural injury has occurred more than 2 years from the surgery date, reinnervation is unlikely to add any benefit secondary to chronic denervation muscle atrophy. The decision-making process becomes more confusing if one schedules the patient for SM within the first year, as we often do. Spontaneous nerve regeneration through an intact but injured nerve may not have had time to manifest itself on EMG. Tucker[7] uses a nerve-muscle pedicle placed through the cartilage window to reinnervate the thyroarytenoid only. This has the potential advantage of leaving the RLN intact for the possibility of regrowth, while providing an alternate neural supply to the thyroarytenoid muscle. These concepts on nerve transfer are only a rough guide. Hopefully, as we obtain longer follow-up on our patients with intraoperative EMG, we can suggest more concrete guidelines.

RESULTS

From April 1987 until April 1992, 116 procedures were performed on 100 patients. There were 123 Silastic implants placed, and 14 AAs performed. Several of these were performed at the same surgical setting and were considered as one procedure. The procedures used are outlined in Table 1.

Primary Silastic Medialization. Thirty-two patients underwent primary SM at the end of the surgical procedure in which the laryngeal innervation was sacrificed. There were 18 men and 14 women ranging in age from 22 to 75 years. Primary AA was performed as well in 3 of the patients. The cause of vagal sacrifice was either a skull base or high vagal nerve tumor in 26 patients, while 5 patients underwent cervical excision of both the carotid artery and vagus nerve secondary to involvement by squamous cell carcinoma (SCC). One further patient, with unilateral paralysis, presented with an extensive anterior cervical osteophyte impinging on the RLN at the cricothyroid junction. Primary SM was performed after the osteophytes were removed. Of this group, 5 patients have undergone surgical revision, 3 with larger implants placed, 1 with both a larger implant

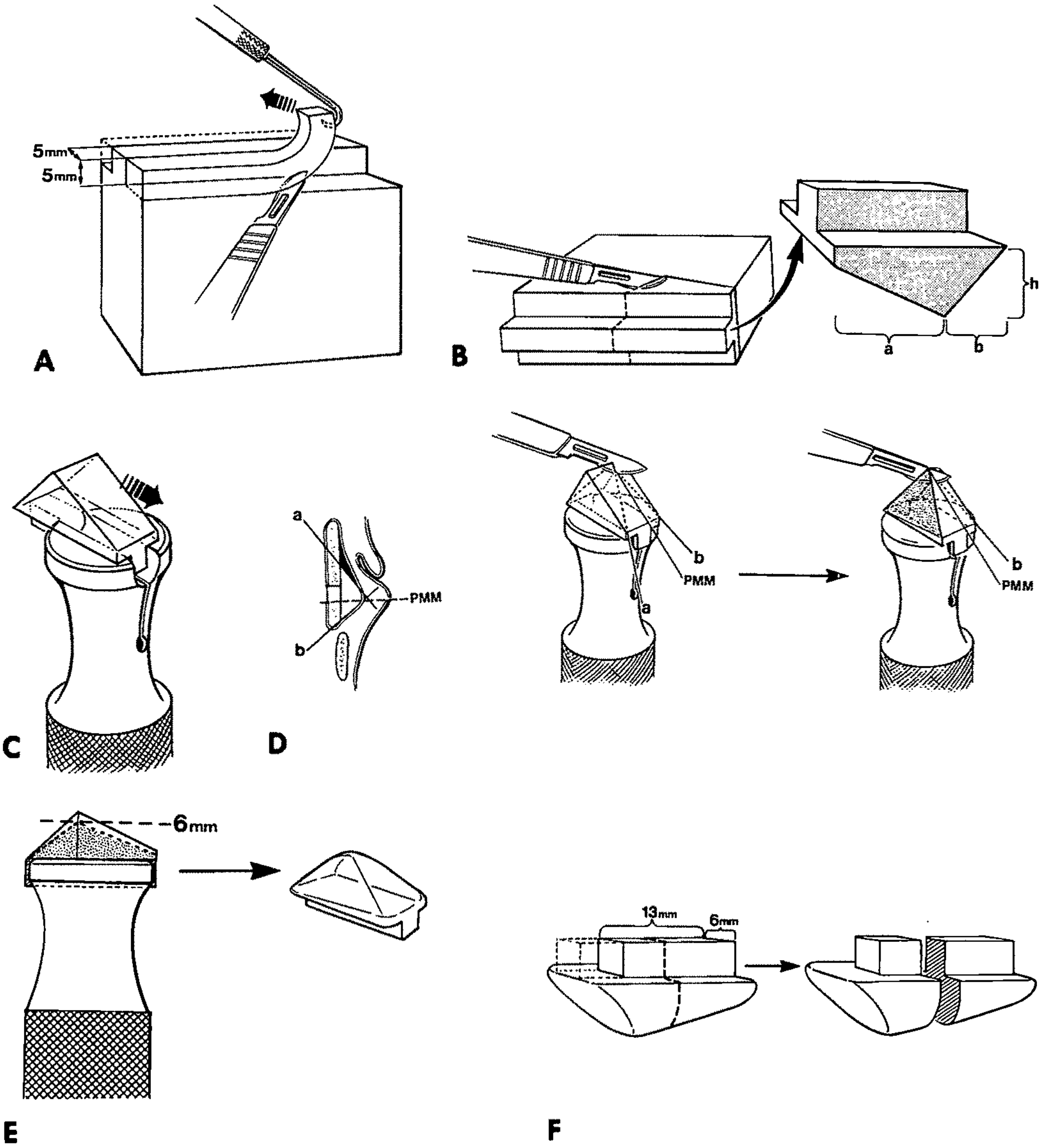

Fig 7. A) Medium-softness Silastic block is prepared by removing two lateral strips, leaving central 5 x 5-mm ridge. B) Rough implant is outlined and cut from block. Distance from front of implant back to point of maximum medialization (a) is determined during voice testing with depth gauge. Residual distance to posterior aspect of implant (b) is 5 mm. Height of rough implant (h) is usually outlined 1 to 2 mm greater than final implant height. C) Rough implant slides into implant holder for final shaping. D) Plane of maximum medialization (PMM) is outlined on implant at level determined by depth gauge during voice testing. This plane is usually at lower level of cartilage window. Excess Silastic is removed from implant by carving from PMM along cuts a and b. E) Final height or medialization point (6 mm in this example) is outlined, and excess Silastic is further removed. All sharp edges are rounded to decrease trauma to paraglottic space during placement of implant. F) After removal from holder, lateral strut is outlined to fit window and excess is removed. Final implant is divided into two pieces to further decrease trauma of insertion.

and AA, and 1 with AA only. One of the first 3 patients with revisions has subsequently undergone a second revision with AA. There have been no graft extrusions in this group.

In the 6 patients who received primary SM secondary to neck surgery, 4 underwent a tracheotomy at the same time to prevent airway compromise after composite resection for SCC. The fifth patient, who underwent radical neck dissection only, and the sixth patient, who underwent resection of the cervical osteophytes, did well with no tracheotomy. Even with early glottal competence provided by the primary SM, 4 of the 5 patients presenting with SCC have performed poorly with swallowing rehabilitation. This is probably due to the surgical alteration of the laryngopharyngeal tissue, as well as the significant sustained edema that accompanies the combination of these ablative procedures and radiotherapy.

Of the 26 patients who received a primary SM secondary to skull base surgery, the first 5 also underwent a tracheotomy. This was standard procedure prior to primary SM to protect the airway from aspiration and provide pulmonary toilet. After we gained confidence in primary SM, the following 21

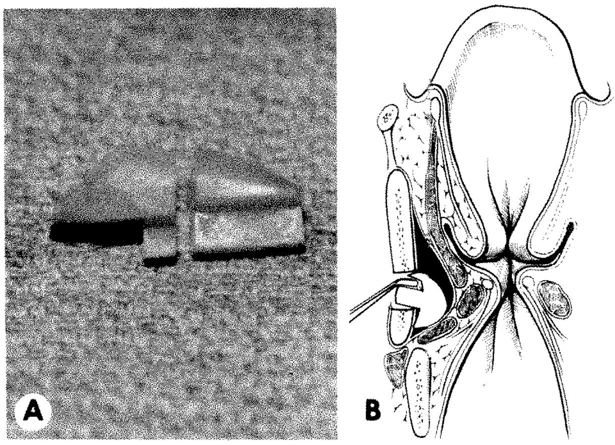

Fig 8. Carved Silastic implant. A) Ready to insert into larynx. It has been divided in half for ease of insertion. B) Lower edge of implant is rolled into window, and upper edge is slowly compressed until it snaps under thyroid cartilage. Posterior half is placed first and moved back into position; anterior piece locks it in place.

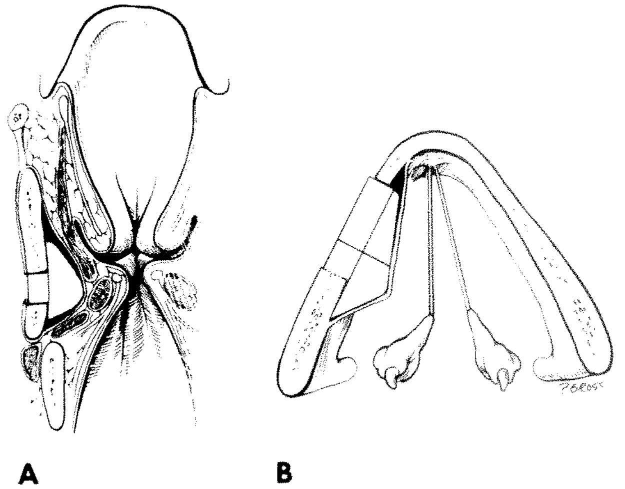

Fig 9. A) Final position of implant demonstrates maximum plane of medialization at lower margin of window to prevent medialization of false cord and ventricle. B) Posterior extension of implant, which can be adjusted, will medialize vocal process of arytenoid in most cases.

patients underwent medialization only at the time of skull base surgery.

Two of these 21 patients subsequently underwent a tracheotomy. The first, a 75-year-old man, lost cranial nerves IX, X, XI, and XII secondary to a complete temporal bone resection for SCC. Cranial nerves IX and X were positive for carcinoma at the brain stem. The patient never regained his preoperative level of mental status. Postoperatively he was lethargic but arousable and underwent a tracheotomy 2 weeks later after severe aspiration pneumonia further compromised his health. He died of his disease 8 months later.

The second, a 56-year-old woman who underwent primary SM along with excision of an extensive vagal paraganglioma, developed increasing stridor postoperatively. On laryngoscopic examination we could see that the implanted cord was nicely positioned in the midline; however, the contralateral TVC was paralyzed as well, necessitating a tracheotomy to relieve airway obstruction. Her clinical course was further complicated by subacute bacterial endocarditis. Two months later, after normal function of the contralateral TVC returned, she was decannulated and oral nutrition was resumed.

The other 19 patients have progressed through their postoperative period without the need for tracheotomy. Initial oral intake and adequate oral intake occurred earlier in these patients who did not undergo a tracheotomy, as compared to patients who underwent tracheotomy alone or tracheotomy along with primary SM. We recently reviewed this group of patients to assess the improvements in postoperative rehabilitation by the use of primary SM.[13] To prevent redundancy, the reader is referred to that work for an in-depth discussion of the results. The voice results in this group are difficult to report objectively. When trained speech evaluators were asked to judge the quality of the voice of these primary SM patients, the quality and projection of the voice was frequently underappreciated because of the hypernasality and articulation deficits resulting from high resection of cranial nerves IX, X, and XII. For this group a simple rating scale included four divisions. Patients with follow-up tapes were evaluated. Fourteen of the 21 patients who returned to Nashville for follow-up were judged to have normal or near-normal voice. Five patients developed either moderate breathiness with good projection or significant raspiness. Two patients had a significant air leak and could not communicate in a loud environment. No patients developed a whisper voice. The voice quality continues to improve for up to 1 year after the procedure. There were no delayed complications in this group.

Secondary Silastic Medialization. Fifty-seven patients underwent secondary SM under local anesthesia. Four of these patients underwent AA as well. This group consisted of 36 men and 20 women who ranged in age from 24 to 85 years. Of this group 8 patients have undergone revision surgery, 4 with larger unilateral implants, 2 with larger implants plus AA, and 2 with AA alone. The causes of the unilateral paralysis or paresis are outlined in Table 2. No stridor developed in any of the patients, either acutely or in the postoperative period. All except 2 presented with unilateral paralysis. One of these 2 was a 31-year-old man who presented with a 2-year history of poor communication with a breathy voice. He was struggling to keep his job as foreman of the night shift at a local factory. The voice alteration occurred after a severe bout of laryngitis. Examination demonstrated bilateral motion with significant notching of the anterior half of the right TVC. After unilateral SM his voice returned to near normal, with excellent projection. The second patient presented with significant

TABLE 1. PHONOSURGICAL PROCEDURES USED FOR GLOTTAL INCOMPETENCE

Procedure	*No.*
Primary unilateral implant	29
Primary unilateral implant with arytenoid adduction	3
Secondary unilateral implant	62
Secondary unilateral implant with arytenoid adduction	7
Arytenoid adduction	4
Bilateral implants	11
Total	116

TABLE 2. CAUSE OF VOCAL CORD PARALYSIS OR PARESIS IN PATIENTS UNDERGOING SECONDARY SILASTIC MEDIALIZATION WITH OR WITHOUT ARYTENOID ADDUCTION

Cause	*No.*
Unilateral paresis	
Laryngitis	1
Idiopathic	1
Unilateral paralysis	
Skull base surgery	10
Chest surgery	10
Chest neoplasm	8
Trauma	4
Recurrent laryngeal nerve avulsion for spastic dysphonia	4
Thyroid surgery	4
Other neck surgery	3
Neck cancer	2
Laryngeal surgery	2
Idiopathic	6
Unknown	2

unilateral paresis; a unilateral implant failed to improve his condition. The arytenoid on the weaker side, although mobile, failed to come to midline. During attempted revision it was obvious that if a large enough implant were placed to medialize the arytenoid, its function would be impaired. This may have been indicated for voice improvement, but not fully understanding the cause of his paresis, we were hesitant to harm unilateral function for fear that the opposite TVC might be affected in a similar manner in the future. The only complication in the series occurred in a man who presented with a lateralized fixed hemilarynx. Fifteen years prior he had undergone radiotherapy to his right TVC for SCC. This resulted in a breathy voice with mild aspiration. During the surgical procedure, after the cartilage window had been removed, the paraglottic space was found to be fibrotic with scar tissue. The ventricle was inadvertently entered during the elevation of this fixed tissue. The operation was completed with perioperative antibiotic coverage. The patient was initially pleased with the voice improvement, but a draining sinus to the skin developed several weeks later. After a lengthy trial of antibiotics failed to bring improvement, the patient refused to allow removal of the implant. Although his voice was very raspy, he was pleased with the improvement in swallowing resulting from the implant. Finally, 6 months postoperatively the implant was removed. He went on to develop chondritis of the thyroid cartilage, which resolved after debridement.

To gain a more objective approach to the analysis of the postoperative voice quality, several different parameters were considered. Although maximum phonation time and mean airflow have a great deal of variation, these may be the best tests to demonstrate improved glottal competence. Our early data were sketchy in this area, and we continued to try to apply these tests in a meaningful way to determine the degree of voice improvement. A subjective review of the available voice tapes using a simple evaluation of postoperative voice yielded 23 patients with normal or near-normal voice, 11 patients with slight breathiness or significant raspiness, 2 patients with weak voice, and no patients with a whisper voice.

In an attempt to better quantify these findings, one of the senior authors (R.E.S.) set up a computer model in which matched pairs of preoperative and postoperative voice samples were recorded on a computer disk. The preoperative and postoperative voice samples of each patient were randomly presented so that the listener was blinded as to whether samples were preoperative or postoperative. The samples were then played in pairs to each of 5 voice listeners. The listeners assigned a value (1 to 50) to the "desirability" of voice quality. Eighteen patients with good-quality preoperative and postoperative tapes were selected from this group. Sixteen of these patients were judged to have a better postoperative voice, while 2 were judged to have a better preoperative voice. The summary of the scores of the 5 judges are shown in Fig 10. A score of 40 or above was judged to show a near-normal or normal voice. This graph demonstrates a significant sustained improvement in a majority of the patients. The correlation between the scores of the 5 judges was very close on most patients, lending a greater validity to the accuracy of the voice score.

Bilateral Silastic Medialization. Eleven patients underwent bilateral SM for glottal incompetence. This incompetence was most often manifested in the patient by a weak, breathy voice along with mild aspiration. The disorders that resulted in this condition are listed in Table 3. There have been no complications in this group. One of the earlier patients developed mild stridor on the first postoperative morning due to bilateral vocal cord edema with slight unilateral intracordal bleeding. After treatment with intravenous steroids and observation, he was asymptomatic within 48 hours. Only 1 of the 11 patients has undergone a revision, with a larger implant placed on 1 side only.

The 6 patients who underwent surgery for presbylaryngis were all improved, with increased volume and projection, as well as improvement in deglutition

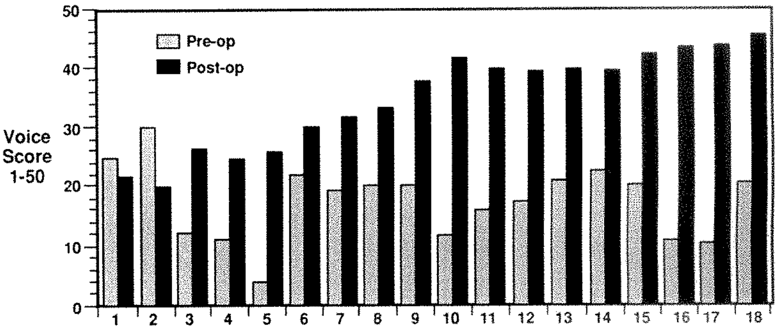

Fig 10. Summary voice scores for preoperative and postoperative voice in 18 patients who underwent unilateral secondary Silastic medialization demonstrate voice improvement in 16 of 18 patients. Voices were rated from 1 to 50 on basis of quality of communication and voice desirability. Scores above 40 were given for normal or near-normal voice.

with decreased aspiration. There were 5 men and 1 woman in this group, with an average of 71 years. The remaining 5 patients, 3 women and 2 men with a mean age of 35 years, were the least improved group in this series.

The configuration in all of these larynges demonstrated bowing of the vocal cords, greater in the posterior third than the anterior aspect of the glottal opening. Moderate improvement with decrease in breathiness was seen in 2 patients, who presented, respectively, with a history of strangulation and severe upper respiratory tract infection.

Minimal differences were seen in the postoperative voice in the remaining 3. The first, who had suffered a cerebrovascular accident secondary to fat embolism, presented with a weak whisper voice and poor articulation. Her examination showed a 2- to 3-mm open posterior glottic chink. Bilateral implants 2 x 5 x 13...10 failed to close the gap, and minimal change in voice was noted. She has, however, continued to gain further volume over the first postoperative year.

The second patient, a 40-year-old man, presented with the same laryngeal configuration, along with slight breathiness in the voice that prevented him from singing. A test with bilateral Gelfoam injections resulted in an excellent, strong voice. Conservative implants were placed bilaterally, but little improvement was seen. He was sent to another center for collagen injections, which also failed to improve the voice.

The final patient presented with a 2- to 3-mm gap between the cords and a spastic, strained quality to the voice. He had received a diagnosis of spastic dysphonia; however, on examination his vocal cords did not touch. We felt that the spastic quality might be a compensation for his glottal incompetence, and he underwent bilateral implants of 2 x 5 x 13...13. He continued to have mild spasticity, but his voice quality improved. In retrospect, larger implants might have been more helpful in these 5 patients. We were very conservative at first, for fear the implant would impair the normal arytenoid movement.

Voice analysis was performed by the panel of listeners judging the random blinded voice pairs, as described, for 8 patients in this category. This is outlined in Fig 11. One of the patients, who had suffered strangulation, was felt to have a worse voice postoperatively. Although the patient felt her communication and especially swallowing function were greatly improved, the quality of her voice was quite variable over time.

DISCUSSION

Many have been the detractors of SM, citing the ease of injection and long-term record of Teflon and implying that SM offers no advantage over the use of Teflon. As we have begun to take a closer look at Teflon, the problems are more evident. Because most otolaryngologists lack adequate experience with this procedure, they doubt that good results can predictably be obtained with Teflon injection. It is difficult to predict the migration of the Teflon during the injection within the TVC. We are beginning to see, with increasing frequency, granuloma formation within the injected TVC, which is devastating to voice quality and eventually causes airway compromise.

We feel that SM has several significant advantages over Teflon. First, good-quality voice results are highly reproducible. Compared to Teflon, the quality of improvement is more predictable, depending on the preoperative condition. Second, it is much easier to train other physicians in its use. It is impossible to teach someone the correct feel for the injection of Teflon into the TVC. This must be learned by experience, which is gained at the expense of patients until the technique has been perfected.

Most often, attending physicians in training programs will personally perform their own Teflon injections, because it is one of the few procedures that if performed wrong is uncorrectable. On the other hand, the techniques and judgments in SM can be readily conveyed to a pupil. All the residents leaving our program are fully trained and comfortable with this procedure.

The real difference in the two procedures is mainly due to the third and fourth advantages of SM, adjustability and reversibility. The adjustability is its single greatest advantage over Teflon. With a depth

TABLE 3. CAUSE OF GLOTTAL INCOMPETENCE IN PATIENTS RECEIVING BILATERAL IMPLANTS

Cause	*No.*
Presbylaryngis	6
Head injury	1
Strangulation	1
Laryngitis	1
Idiopathic	2
Total	11

gauge, the medialization can be simulated prior to implant placement, allowing for the rapid testing of multiple positions of cord displacements to acquire the best voice. If further adjustments are needed after the implant placement, it can be removed, adjusted, and replaced as necessary. The reversibility not only allows for future adjustments for anatomic or functional changes that may result in a weaker voice over time, but also allows for its use in several settings that are unsuitable for Teflon. First, it is inappropriate to inject Teflon in patients who have an intact vagal-RLN system who present within the first year of the paralysis, if there is any chance that vocal cord function may return. If vocal cord movement returns, the Teflon would prevent normal function of the injected cord. An exception to this would be in the terminally ill patient who might benefit from the brevity of the procedure for Teflon medialization. Because of the reversibility of SM, it can be placed relatively safely within this first year, as the severity of the symptoms dictate, in the knowledge that removal of the implant is possible if function returns. Second, it can be placed deep to a mobile TVC, augmenting the adducted TVC position without significant effect on its motion or vibratory function.

Besides voice improvement, the second major benefit of cord medialization is improvement in deglutition with a decrease in aspiration. Even if the voice was not brought back to its normal premorbid state, aspiration was universally improved. In 3 patients who had previously suffered a cerebrovascular accident from either a traumatic head injury or a postoperative complication from a neurosurgical procedure, the voice results were disappointing. Although the projection and the volume that developed were reasonable, the oropharyngeal incoordination led to such poor articulation that it shadowed the voice improvement. Aspiration, however, was significantly improved in all 3.

A consistent pattern of voice improvement has been seen in most patients. The initial voice improvement acquired on the operating table rapidly changes in the recovery room as perioperative edema develops. Although the voice is usually much stronger, it is raspy for several days to weeks after surgery. Often, however, the voice quality is quite good within the first week after surgery. Surprisingly, a second raspy phase occurs at 4 to 6 weeks after surgery. This usually subsides, however, within 2 more weeks. Voice quality continues to improve in some patients for up to 1 year after surgery. Because of this postoperative cycle, voice samples recorded before 3 months after the date of surgery may not be representative of the long-term voice quality. It is important to inform patients and their family of this postoperative voice cycle, to prevent disappointment with their voice results over the first several postoperative months.

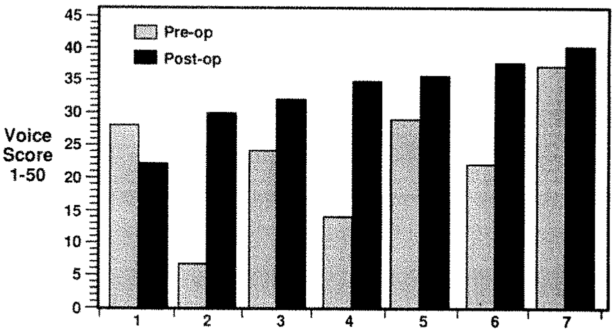

Fig 11. Results of "desirability rating" are outlined for preoperative and postoperative voice scores in 7 patients who underwent bilateral Silastic medialization.

There are only 2 relative contraindications to SM. First, patients who have previously undergone a vertical hemilaryngectomy often develop a weak, breathy voice. Teflon injection has been recommended to augment the scarred surgical side to improve glottal closure. We were consulted to perform a revision in 1 such patient who had developed no voice improvement from SM after a vertical hemilaryngectomy. Without the buttress of the thyroid cartilage there is probably not enough lateral support for the Silastic implant to hold the scarred band of the larynx in a medialized position. Thus, placement of an implant would only lateralize the cervical soft tissue, rather than effecting medialization of the scarred side of the larynx. Second, previous laryngeal irradiation is a relative contraindication. If the larynx is still soft and supple, with minimal scarring, then careful surgery may be indicated. If the ventricle is violated during the procedure, placement of the implant should be delayed until mucosal healing has occurred.

The ansa-RLN transfer and SM have been compared as mutually exclusive procedures for repair of unilateral paralysis.[14] We, however, perceive the ansa-RLN transfer and SM not as alternate procedures exclusive of each other, but as surgical companions, both functioning by different mechanisms to conjointly return laryngeal function to its normal state. Even with excellent initial success with SM, if the laryngeal muscles are denervated, the atrophy of the muscles may lead to delayed glottal incompetence within 1 to 2 years in the postoperative period. In any patient undergoing SM within the first year of paralysis, whose vagus nerve or RLN is known to be sectioned, an ansa-RLN is now performed if spontaneous reinnervation cannot be demonstrated by EMG. After skull base surgery in which the vagus and hypoglossal nerves are sacrificed, the posterior branch of the ansa arising from the cervical plexus can be used for neural anastomosis with the RLN. Since we have less than 1 year's follow-up on the group of patients who have undergone nerve transfer, it will be several years before we can make significant statements based on the results of the procedure.

Primary SM under general anesthesia is a natural outgrowth of Silastic medialization performed under local anesthesia. The main reason for initiation of its use in this fashion was to eliminate the need for tracheotomy and to decrease the postoperative rehabilitation phase of patients undergoing loss of multiple cranial nerves at the time of skull base surgery. It is obvious that immediate glottal competence in the early postoperative period will allow for better pulmonary protection,with earlier swallowing rehabilitation. This immediate glottal competence also decreases the need for tracheotomy in most skull base procedures in which the pharynx has been denervated and not surgically altered. Tracheotomy, which is often performed in this situation for airway protection, causes significant problems in deglutition secondary to laryngotracheal fixation to the skin and reflex TVC hypomotility secondary to the decrease in laryngeal airflow. Thus, the combination of immediate glottal closure from the primary implant and the prevention of the complications caused by tracheotomy significantly improves the postoperative rehabilitation effort.

A conservative approach was taken initially with primary SM. The first implants were made small for fear of causing airway obstruction. The laryngeal edema that develops from intubation over a 12-hour period added further concern to the potential for airway compromise. However, in time, with no postoperative obstruction due to the implants, they have been enlarged to the same size as secondary implants placed for the same laryngeal configuration. One patient, who was very short and heavy, developed peripheral edema over her 11-hour procedure. She was left intubated for 4 days until the edema subsided and then was extubated; no airway complications were noted postextubation. Prior to primary SM, a preoperative computed tomography scan can aid in identifying thyroid cartilage anatomy and help to predict implant size. In patients with a more obtuse larynx, most often women, the implant is approximately 2 x 5 x 15...10 mm. In the more acute-angled larynx, most often seen in men, the window is placed further back, as previously described. The average size of the the implant is 2 x 6 x 18...13 mm. The initial postoperative voice, although strong, is usually hoarse for several weeks. We continue to see voice improvement for up to 1 year after all of these procedures. Of the 6 revisions performed in this group, 4 were to enlarge some of the earlier small implants. The usefulness of AA in conjunction with these patients will be discussed later.

The degree of improvement of voice quality has not been as consistent in patients presenting with presbylaryngis or bilateral bowing of different causes. Even though the results were not as good as we had hoped, the presbylaryngis patients were quite satisfied with the voice improvement. The major preoperative complaint in this patient group was the inability to communicate well over the telephone or in any public setting with background noise. All patients reported a significant improvement in their communication skills. The second most frequent complaint, mild aspiration, was significantly improved also. This was judged from the patients' history only, with no preoperative or postoperative swallowing tests. Earlier in the series, undersize implants were placed for fear of interfering with arytenoid movement. These early patients have not developed as much volume as the later patients. One of the earlier patients underwent a revision replacing one of his original implants,which was 2 x 4.5 x 13...13 mm, with a new implant that was 2 x 7 x 15...13 mm. This resulted in moderate voice improvement. He may undergo replacement of the opposite, smaller implant in the future. The posterior slope of the implant is designed so that there is no interference with the rocking motion of the arytenoid in and out of the larynx. A man with a large larynx underwent bilateral implants that were 2 x 6.5 x 15...13 mm, with no alteration of arytenoid function. When the larynx is viewed postoperatively in the fully abducted position, one can appreciate the mild decrease in glottal opening secondary to the implant. This decrease, however, is not symptomatic in the geriatric population in which presbylaryngis develops.

A review of the other 5 patients presenting with bilateral bowing not secondary to presbylaryngis is less encouraging. Although initial improvements were minimal in the patients who presented with strangulation and paresis secondary to a severe upper respiratory tract infection, both have shown further improvement over the course of 2 years. It is difficult to know whether this improvement should be credited to the implants or to a slow resolution of the underlying problem. A posterior glottal opening of 3 mm was initially seen in a 30-year-old patient who had undergone a stroke secondary to fat embolism. This posterior glottic gap is probably secondary to incomplete adduction of the vocal processes of the arytenoid. These are difficult to medialize without interference with the arytenoid function. Medializing the paraglottic tissue failed to improve this patient or the two middle-aged patients who presented with idiopathic TVC bowing. Oropharyngeal discoordination and articulation problems, often seen after head injury or stroke, further obscure any improvement in voice that is acquired from the implant. Although we were initially discouraged with the results in this group, the numbers are far too small to draw any conclusions.

The choice to use AA is not as clear-cut as that of SM. In theory, AA would add tension and help bring the vocal cord into a more physiologically correct phonating position. However, the complex interaction of the intralaryngeal muscles, which results in adduction of the arytenoids, is impossible to simulate with a single suture pulling forward on the muscular process. Our experience with 14 patients undergoing AA alone or in conjunction with SM is again too limited to draw more than early inferences. The recommended indications for AA are 1) a very wide glottal chink in which the vocal processes do not come into contact during phonation and 2) a difference in the level of the TVCs during phonation. Certainly, AA is useful in closing a wide glottic gap, but it is not always necessary. We use AA only after the intraoperative evaluation demonstrates incomplete closure of the larynx with SM. In several patients in whom the adjunctive use of AA was anticipated, the Silastic implant alone, with its posterior extension, was able to medialize the posterior commissure very well. If the posterior commissure is still open after SM has been performed, we progress to AA.

In Isshiki's original description, the joint capsule of the cricoarytenoid joint was opened prior to the AA. We routinely performed this in our earlier cases. Although the initial voice result was good, the postoperative video demonstrated overmedialization of the vocal process, which may represent subluxation of the arytenoid into the larynx. In spite of continued good vocal projection, all these patients have developed raspiness of the voice. The joint capsule was opened in only 1 of the more recent 10 patients. Joint fixation in this patient necessitated drilling open the joint with a microcutting bur in order to accomplish adduction. This patient's voice never returned to normal, but significant improvements occurred in the form of increased volume and decreased aspiration. None of the remaining 9 patients have developed raspiness at this time. In this group the average follow-up is 16 months. Arytenoid adduction is an excellent addition to SM for selected patients. Long-term follow-up with voice analysis will be necessary to indicate its real usefulness.

SUMMARY

After this complete review of our first 100 patients undergoing SM and/or AA, we are very encouraged with the improvements in communication derived from these two procedures. The addition of ansa-RLN transfer, when indicated, may prevent muscle atrophy and further sustain the initial voice improvement. These procedures, however, are still in their infancy in regard to development. There is still much to be learned from long-term follow-up of these patients in a multicenter cooperative effort to compare results, performed as the surgical techniques continue to improve.

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SURVIVAL OF SCARPA'S GANGLION IN THE PROFOUNDLY DEAF HUMAN

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The electrically evoked auditory brain stem response in some cochlear implant patients may be confounded by evoked potentials generated by vestibular neurons. The magnitude of this contribution to the response from the vestibular system is unknown, in part because the survival of cells within Scarpa's ganglion in profoundly deaf humans is unknown. Therefore, we undertook a quantitative study of Scarpa's ganglion in 48 deaf subjects who in life would have been candidates for cochlear implantation and in 5 subjects with normal hearing. The numbers of residual cells in both Scarpa's ganglion and the spiral ganglion in deaf subjects were significantly less than in individuals with normal hearing. Bivariate analysis demonstrated a highly significant positive correlation between cell counts of Scarpa's ganglion and the spiral ganglion. The durations of hearing loss and of profound deafness were negatively correlated with Scarpa's ganglion cell counts. However, in contrast to spiral ganglion cell survival, the cause of profound deafness did not predict the number of Scarpa's ganglion cells. Multiple linear regression analysis using a variety of clinical parameters demonstrated that the best predictor of the number of Scarpa's ganglion cells in profoundly deaf humans was the number of remaining spiral ganglion cells.

KEY WORDS — cochlear implantation, Scarpa's ganglion, sensorineural hearing loss, spiral ganglion.

INTRODUCTION

Electrically evoked auditory brain stem response (EABR) has been used to assess the electrical stimulability of surviving auditory neurons in patients considered for cochlear implantation. However, its ability to predict auditory neuronal survival is limited by problems related to response artifacts and stimulus spread to nonauditory pathways. Previous studies in both humans and animals have shown that electrical stimulation of the cochlea may produce evoked potentials generated by vestibular neurons.[1-3]

There have been several quantitative studies of the human Scarpa's ganglion in individuals with no known auditory or vestibular disorders and with certain diseases such as diabetic neuropathy, Meniere's disease, and familial dysautonomia.[4-9] However, the survival of cells within Scarpa's ganglion in the profoundly deaf human has not been previously described. Therefore, a quantitative study of Scarpa's ganglion was performed in 48 profoundly deaf human subjects who in life would have been candidates for cochlear implantation, and in 5 individuals who in life had normal hearing. The correlation between the survival of cells in Scarpa's ganglion and the spiral ganglion in deaf ears was evaluated. Clinical parameters, including the cause of deafness, age at death, duration of hearing loss, and duration of profound deafness, were correlated with cell counts in Scarpa's ganglion and the spiral ganglion. By means of a multiple regression model, possible predictors of the survival of Scarpa's ganglion in profoundly deaf subjects were evaluated.

MATERIALS AND METHODS

Ninety-three temporal bones from 66 patients with documented profound sensorineural hearing loss were identified in the temporal bone collection of the Massachusetts Eye and Ear Infirmary. Counts of surviving spiral ganglion cells in these specimens have been previously reported.[10] One ear from each patient was randomly chosen for study. Of these, 18 were excluded because of artifactual partial or complete absence of Scarpa's ganglion. Therefore, a total of 48 temporal bones from patients with profound sensorineural deafness and 5 temporal bones from individuals with normal hearing were included in the study. The distribution of the profoundly deaf subjects within 12 diagnostic categories is presented in Table 1.

The specimens were fixed in Heidenhain-Susa solution, decalcified in trichloroacetic acid, and embedded in celloidin. All specimens were sectioned in a horizontal plane at a thickness of 20 µm. Every 10th section was stained with hematoxylin and eosin and mounted for light microscopic examination. Scarpa's ganglion cells and spiral ganglion cells were counted by using the methods of Richter[5] and Schuknecht,[11,12] respectively.

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TABLE 1. CAUSES OF PROFOUND HEARING LOSS IN 48 SUBJECTS IN STUDY

Diagnostic Group	*No.*	*Mean Age (y)*	*Diagnosis*
1	8	53	Postnatal viral labyrinthis
2	2	12	Congenital rubella syndrome
3	4	53	Sudden idiopathic deafness
4	1	48	Congenital syphilis
5	5	70	Bacterial labyrinthitis
6	5	55	Neoplasm (cerebello-pontine angle tumor)
7	2	68	Otosclerosis
8	9	41	Genetic cause
9	4	57	Temporal bone fracture
10	5	27	Aminoglycoside toxicity
11	1	76	Meniere's disease
12	2	79	Unknown cause

TABLE 2. MEAN CELL COUNTS FOR SCARPA'S GANGLION AND SPIRAL GANGLION

		Scarpa's Ganglion		*Spiral Ganglion*	
	No.	*Mean*	*SD*	*Mean*	*SD*
Diagnostic group					
1	8	13,574	3,246	7,879	5,760
2	2	11,676	3,279	13,127	261
3	4	12,440	7,304	19,319	13,424
4	1	4,779		3,672	
5	5	12,796	4,003	11,615	5,230
6	5	10,930	6,278	17,710	9,047
7	2	12,803	8,369	16,223	83
8	9	10,364	6,350	11,767	5,926
9	4	7,481	5,407	11,468	9,152
10	5	14,948	3,264	23,267	5,607
11	1	12,447		14,904	
12	2	8,550	10,920	7,837	5,870
Mean		11,630	5,384	13,500	8,115
Normal-hearing group					
	5	16,862	2,145	27,304	4,203

Statistical analyses were performed with both SAS (SAS Institute, Cary, NC) and BMDP (University of California, Los Angeles, Calif) software. The mean totals of cells for subjects within each of the 12 diagnostic categories and for five normal-hearing individuals were determined. Differences in mean total counts of the populations in the deaf group and the nondeaf group were analyzed by Student's *t* test. Pearson's r was calculated to assess the correlation between the counts of Scarpa's ganglion cells and spiral ganglion cells. In addition, neuronal counts were correlated with other clinical variables, including age at death, age at onset of total deafness, duration of deafness (age at death minus the age at onset of deafness), age at onset of hearing loss, and duration of hearing loss (age at death minus the age at onset of hearing loss).

The differences in mean totals of Scarpa's ganglion cells between pairs of diagnostic groups and between diagnostic groups and the nondeaf group were submitted to an analysis of variance followed by *t* tests. The Bonferroni approach was used to adjust the p values for multiple comparisons at the .05 level of significance.

Multiple linear regression analysis was performed to assess the variables related to survival of Scarpa's ganglion cells in profoundly deaf subjects while adjusting for the effects of diagnostic groups.

RESULTS

The means and standard deviations of total Scarpa's ganglion and spiral ganglion cells within the 12 diagnostic groups of profoundly deaf subjects and five individuals with normal hearing are presented in Table 2. There was a significant difference between the deaf and the nondeaf groups in survival of Scarpa's ganglion cells (p = .016) and of spiral ganglion cells (p = .0005). This finding was corroborated by plotting the two neuronal counts in different diagnostic groups with at least four subjects as shown in Fig 1. There was a positive correlation between the two neuronal counts in different diagnostic groups, although groups 1 and 5 (viral and bacterial labyrinthitis groups) appeared to be outliers.

The Bonferroni approach showed no significant differences in mean total Scarpa's ganglion cell counts for pairs of diagnostic groups, in contrast to the findings for total spiral ganglion cell counts.[10]

Bivariate analyses of total Scarpa's ganglion cell counts and a number of clinical variables are presented in Table 3. There was a significant correlation between Scarpa's and spiral ganglion cells in profoundly deaf humans (r = .541, p = .0001). Although the number of residual spiral ganglion cells decreased with longer duration of hearing loss (p = .003) and duration of profound deafness (p = .005), Scarpa's ganglion cell counts did not demonstrate similar correlations with these variables.

Bivariate analyses of total Scarpa's ganglion cell counts with spiral ganglion cell counts and the clinical variables were repeated for a subgroup of 27 deaf subjects after diagnostic groups 1 and 5 (with 13 subjects) were excluded. The rationale for exclusion of groups 1 and 5 from this analysis was based on evidence that counts of the remaining cells in these two groups were different from those of all other diagnostic groups. First, as shown in Fig 2, although the majority of diagnostic groups had nearly the same percentage of cells remaining as age-matched normals, the patients with a presumptive diagnosis of laby-

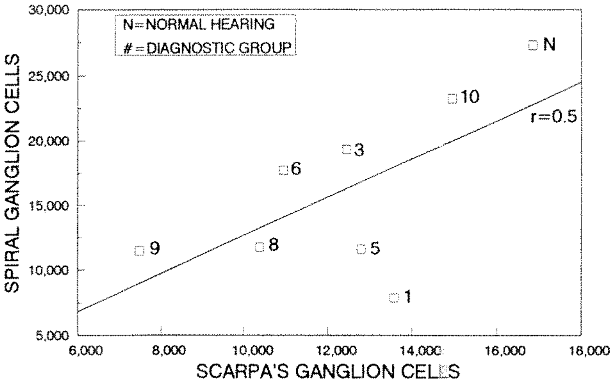

Fig 1. Means of Scarpa's ganglion cell and spiral ganglion cell counts in several diagnostic groups (see Table 1 for definition).

rinthitis (viral or bacterial), from groups 1 and 5, had greatly reduced spiral ganglion cells (28% to 40%; compared to about 80% survival of Scarpa's ganglion cells). Second, a multiple regression analysis of the difference between spiral ganglion cell and Scarpa's ganglion cell counts across diagnostic groups showed that group 1 was not significantly different from group 5, but that it was significantly different from other groups with at least 4 subjects. When these two groups were excluded, a stronger correlation between Scarpa's ganglion cells and spiral ganglion cells was found (r = .696, p = .0001). In addition, the duration of hearing loss and duration of profound deafness were also significantly correlated with both the Scarpa's ganglion cell count and the spiral ganglion cell count.

Finally, because these clinical variables may not be independent and the cause of deafness may be a confounding variable, multiple regression analysis was performed with data from 40 deaf ears from groups with at least four subjects. In this analysis, only sex, age at death, and age at onset of deafness were included in the regression model, as duration measures would be linearly related. The major correlate of survival of Scarpa's ganglion cells in profoundly deaf subjects was the residual number of spiral ganglion cells (p = .0001).

DISCUSSION

The numbers of residual cells in Scarpa's ganglion and the spiral ganglion in deaf patients were significantly less than those in five individuals with normal hearing. There was a significant positive correlation between these two neuronal populations in the profoundly deaf human subjects, particularly when patients with a presumptive diagnosis of viral or bacterial labyrinthitis (diagnostic groups 1 and 5) were excluded from the analysis. Although the number of spiral ganglion cells was significantly influenced by the cause of deafness, duration of hearing loss, and duration of profound deafness,[10] in the present study, the survival of Scarpa's ganglion cells was correlated negatively only with the duration of hearing loss and the duration of profound deafness in a subgroup of deaf subjects (n = 27). However, when multiple regression analysis was done to control for the etiologic effects, it was found that the major correlate of Scarpa's ganglion cell survival at death in profoundly deaf humans is the residual number of spiral ganglion cells. The number of subjects in each diagnostic group may be a limiting factor that masks the possibility that cause of deafness could be an important predictor of Scarpa's ganglion cell survival in a subset of profoundly deaf humans.

TABLE 3. PEARSON CORRELATION COEFFICIENTS FOR SEVERAL CLINICAL VARIABLES AND CELL COUNTS

	Scarpa's Ganglion		*Spiral Ganglion*	
	Coefficient	*p*	*Coefficient*	*p*
Scarpa's ganglion			.541	.0001
Sex	.037	.803	−.095	.523
Age at death	−.180	.221	−.257	.078
Age at onset of deafness	.066	.663	.066	.660
Duration of deafness	−.214	.153	−.407	.005
Age at onset of hearing loss	.017	.911	.201	.176
Duration of hearing loss	−.185	.213	−.429	.003

A comparison of the survival of Scarpa's ganglion cells and spiral ganglion cells in the same individuals allows us to examine the relative behavior of the two neuronal populations in subjects profoundly deafened by various causes and also to assess the factors affecting survival. The finding that the cause of deafness more significantly affected the numbers of surviving spiral ganglion cells than the numbers of Scarpa's ganglion cells may be explained by differential sensitivity of portions of the labyrinth. A theory of Guggenheim,[13] further developed by Schuknecht et al,[14] maintains that the phylogenetically older pars superior (utricle and semicircular canals) is less susceptible to a variety of insults than the younger pars inferior (cochlea and saccule). Differential sensitivity of the two divisions is also seen in an animal model of genetically induced profound sensorineural hearing loss, in which there is little degeneration of Scarpa's ganglion despite marked loss of spiral ganglion cells.[15] In addition, there may be significant differences in the rate of degeneration of neurons in the peripheral vestibular and auditory systems. For example, vestibular ganglion cell loss following hair cell degeneration due to aging progresses slowly over about 30 years.[5] Similarly, the number of Scarpa's ganglion cells in patients with other causes of vestibular hair cell degeneration was not significantly different from that in age-matched controls.[8,9] How-

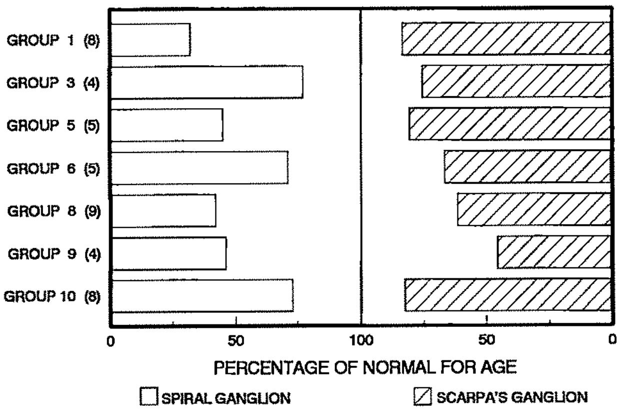

Fig 2. Survival of Scarpa's ganglion and spiral ganglion cells expressed as percentage of normal cell counts for age. See Table 1 for definition of diagnostic groups. Numbers in parentheses are numbers of subjects.

ever, the positive correlation between the two neuronal populations implies that Scarpa's ganglion cells are susceptible to certain factors that may cause degeneration of spiral ganglion cells, despite the absence of significant correlations between clinical parameters and survival of Scarpa's ganglion cells in this study. For example, anatomic contiguity may predispose both auditory and vestibular ganglion cells to degenerative changes in cases of temporal bone fracture and in neoplasms of the cerebellopontine angle, as suggested by data from diagnostic groups 6 and 9, which showed survival in the two ganglia to be very similar.

The relatively poor correlation between the number of surviving Scarpa's ganglion cells and that of spiral ganglion cells for diagnostic groups 1 (postnatal viral labyrinthitis) and 5 (bacterial labyrinthitis) may possibly be explained by the greater susceptibility of the pars inferior (cochlea and saccule) to infectious or inflammatory processes.[14]

The EABR has been observed in some cochlear implant patients to be confounded by evoked signals from the vestibular system.[1,2] The absence of nonauditory percepts such as vertigo or dizziness did not preclude the observation of these potentials. There is a resemblance noted between these potentials and those early negative responses obtained with direct vestibular nerve section in cats.[1] In addition to this early negative component of the EABR, a later, ocular muscle response has been observed after intracochlear stimulation in the rat.[3] In all these studies, a relationship with the vestibulo-ocular reflex has been postulated. The data in the study by Hall[3] suggested that activation of the saccule or the saccular nerve may be responsible for the vestibulo-ocular potentials, but the evidence is still inconclusive. Moreover, it seems likely that activation of vestibular afferents would contribute to the compound action potential of the cochlear nerve, but the data currently available in the rat suggest that such a contribution is very small.[3]

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ATELECTASIS OF THE MAXILLARY SINUS WITH ENOPHTHALMOS AND MIDFACE DEPRESSION

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Enophthalmos previously has been reported to be a rare complication of maxillary sinus mucoceles. We report three patients treated by the senior author (T.C.C.) over a 2-month period for enophthalmos or obvious deformity of the midface associated with complete opacification of the maxillary antrum. Most previous authors have stressed the role of chronic pressure necrosis or osteitis leading to bone destruction, with primary involvement of the orbital floor. No patients in this series had symptoms typical of maxillary sinus mucoceles. Two of our three patients presented with minimal symptoms of chronic infection. There was inward collapse of the anterior, superior, lateral, and medial walls of the maxillary sinus, with no radiographic or intraoperative confirmation of bone destruction. We speculate that this process may be the result of chronic maxillary hypoventilation with subsequent atelectasis of the antrum secondary to chronic negative pressure. All patients had obstruction at the osteomeatal complex and were treated by endoscopic enlargement of the natural maxillary ostium.

KEY WORDS — endoscopic sinus surgery, enophthalmos, maxillary sinus atelectasis.

INTRODUCTION

Spontaneous enophthalmos was first reported to be a rare complication of maxillary sinus mucoceles by Montgomery[1] in 1964. In the largest series published to date, Wilkins and Kulwin[2] reported five patients who were found to have intraoperative destruction of the orbital floor with antral prolapse of the periorbita. It was proposed that chronic pressure necrosis and osteitis led to bone resorption or demineralization of the orbital floor, resulting in enophthalmos. We report a series of three patients presenting over a 2-month period with enophthalmos and complete maxillary sinus opacification. High-resolution computed tomography (CT) failed to reveal evidence of bone destruction in two patients. The CT results were equivocal in the third case, but the walls of the sinus were found to be intact on surgical exploration. All three patients had generalized collapse of the antral cavity with inward bowing of the superior, anterior, lateral, and medial sinus walls. We speculate that this process developed as a result of chronic antral hypoventilation secondary to obstruction of the osteomeatal complex with subsequent atelectasis of the sinus. We managed this problem by endoscopic enlargement of the natural ostium to reestablish maxillary ventilation.

CASE REPORTS

Case 1. A 50-year-old woman first noticed right malar depression while viewing photographs taken of herself on Christmas, 1990. In November 1990 she had developed a pressure sensation over the right maxillary sinus with frequent sneezing and coughing. A CT scan of the paranasal sinuses was obtained in June 1991 that showed complete opacification of the right maxillary and frontal sinuses, with significant posterior bowing of the anterior maxillary wall, ptosis of the right orbital floor, and medialization of the lateral maxillary wall (Fig 1).

At operation the right middle turbinate was found to be lateralized and was infractured to allow passage of the Storz endoscope into the middle meatus. The patient underwent endoscopic ethmoidectomies and sphenoid sinusotomies using a modified Messerklinger technique, with enlargement of a right middle meatus antrostomy. Pathology showed evidence of chronic inflammation. Postoperatively she was treated with saline nasal irrigation and topical steroids. There was no progression of her malar depression or enophthalmos during a 17-month postoperative follow-up.

Case 2. A 41-year-old-woman with a 10-year history of recurrent nasal allergies and sinusitis developed diplopia and right eye chonic irritation in May 1991, shortly after completing a course of oral antibiotics for an exacerbation of her sinusitis. She was evaluated by her ophthalmologist, who found 3 mm of right enophthalmos not noted on previous examinations. In 1985 she had undergone plain film sinus x-ray studies and head CT that showed well-

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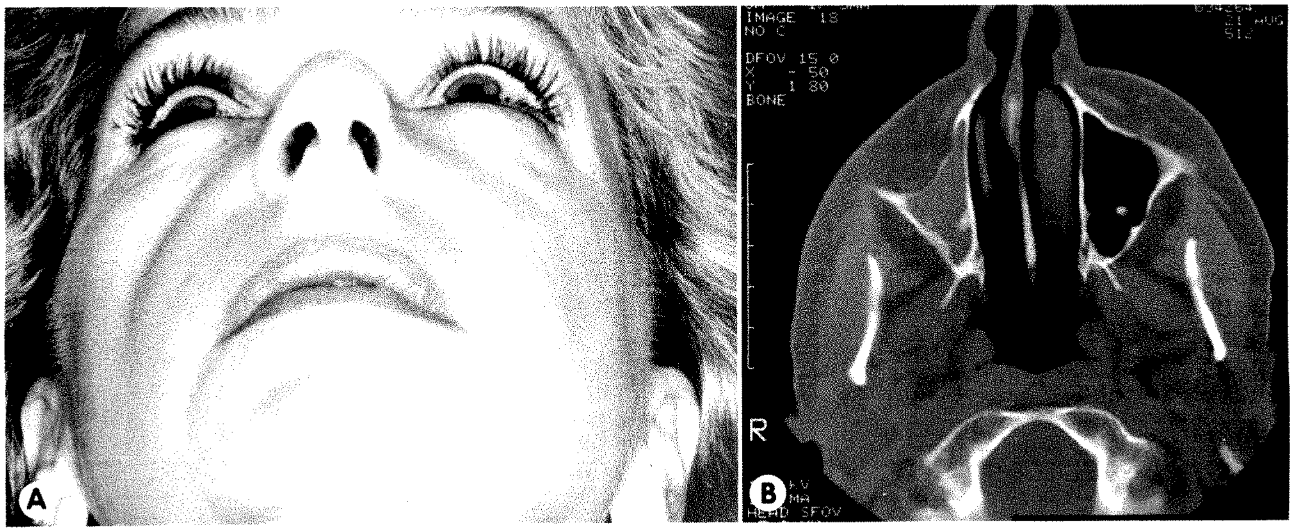

Fig 1. (Case 1) A) Depression of right malar eminence and enophthalmos. B) Axial computed tomogram shows complete opacification of right antrum with posterior bowing of anterior maxillary wall.

aerated, symmetric maxillary sinuses. A CT scan of the paranasal sinuses was performed in August 1991 that revealed chronic bilateral frontal and ethmoid sinusitis with complete opacification of the right maxillary sinus. The right orbital floor was intact but sagging into the antrum, with subsequent enlargement of the right orbit accounting for the enophthalmos (Fig 2). The right middle turbinate was radiographically interpreted to be absent, but endoscopic examination showed the turbinate to be adherent to the lateral nasal wall.

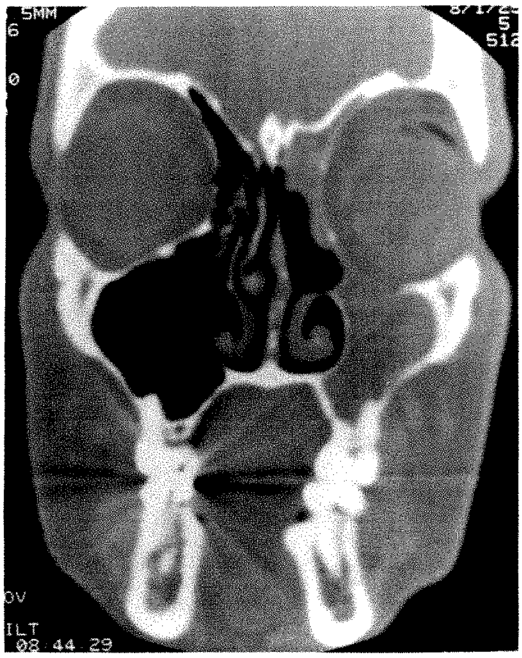

Fig 2. (Case 2) Coronal computed tomogram showing right enophthalmos with contraction of opacified maxillary sinus. Right middle turbinate cannot be discerned from lateral nasal wall. Transverse dimension of sinus at level of floor of nose is 16 mm on involved side versus 23 mm on uninvolved side.

The patient underwent endoscopic ethmoidectomies and sphenoid sinustomies with creation of middle meatus antrostomies in September 1991. The right middle turbinate was medialized to provide access to the right middle meatus. She has not experienced recurrent disease during a 15-month postoperative period.

Case 3. A 42-year-old man became aware of right-sided enophthalmos when it was brought to his attention by a family member who had not seen him for some time. On presentation to an ophthalmologist, his enophthalmos was evaluated with a CT scan of the orbits and paranasal sinuses that showed complete opacification of the right maxillary sinus with inferior displacement of the orbital floor and possible bony erosion of the posterior lateral sinus wall (Fig 3). Inflammatory sinus disease was also seen in the frontal and ethmoid sinuses. Despite these radiographic findings, the patient had a paucity of typical sinusitis complaints, limited to intermittent morning rhinorrhea, sneezing, and right-sided nasal obstruction. There was no history of trauma.

The patient underwent endoscopic ethmoidectomies with creation of middle meatus antrostomies in September 1991. Because of the atypical presentation and possible bone erosion on CT, a right-sided Caldwell-Luc approach was used to explore the maxillary sinus to rule out neoplasia. All walls of the sinus were found to be intact, with no bone erosion. He has done well during a 15-month follow-up period.

DISCUSSION

In 1964, Montgomery[1] first reported on two pa-

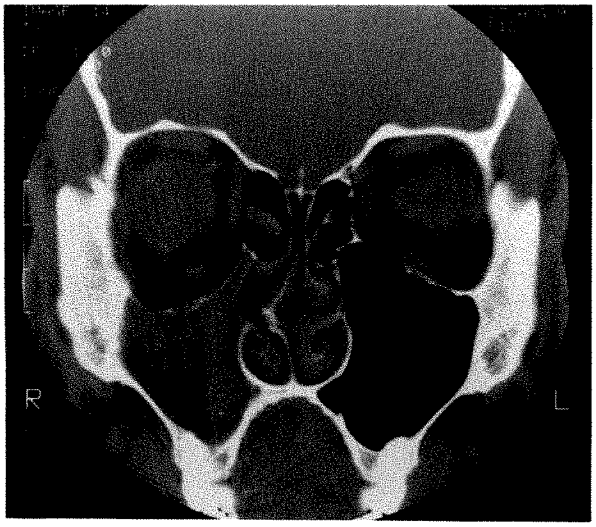

Fig 3. (Case 3) Coronal computed tomogram showing right maxillary opacification and sagging of right orbital floor. Transverse dimension of involved sinus at level of floor of nose is 5 mm less than on uninvolved side. Right middle turbinate cannot be discerned from lateral nasal wall.

tients with complete maxillary opacification who presented with enophthalmos. Since that time most authors have reported bone resorption or destruction of the orbital floor as the etiologic factor in the development of maxillary sinus atelectasis.[2-5] Most previous reports suggest that pressure necrosis occurs along the orbital floor secondary to an expansile maxillary sinus mucocele, with subsequent prolapse of the orbital contents into the maxillary antrum. Antral mucoceles typically present as a gradually expanding mass associated with proptosis, ptosis, epiphora, numbness of the cheek, bloody nasal discharge, cheek fullness, maxillary pain, nasal obstruction, or loose teeth.[6] In our series of patients, these symptoms were conspicuously absent, and there was no radiographic or intraoperative confirmation of bone loss. Rather there was general inward collapse of the anterior, lateral, and medial walls of the antrum in addition to bowing of the orbital floor. Our observations are supported by two previous case reports in which the bony walls of an atelectatic sinus were found to be remodeled but intact.[7,8]

Our observations seem to indicate that atelectasis of the maxillary sinus arises from obstruction of the natural ostium within the middle meatus. Unlike those in a previous report,[9] all three of our patients had obstruction of the middle meatus by a severely lateralized middle turbinate, to the extent that the middle turbinate could not be resolved from the lateral nasal wall on coronal CT. We speculate that hypoventilation of the maxillary sinus could lead to the development of negative pressure as occurs in the middle ear, with subsequent development of effusion and inward collapse of the thin sinus walls. This process seems to be distinct from the events that occur during development of antral mucoceles. Infectious sinusitis with osteitic destruction of the orbital floor also seems to have a limited role in the development of maxillary sinus atelectasis, as only one of our three patients reported a history of symptoms typical of infectious sinusitis. This would seem to be supported by the observation that previous cultures taken from atelectatic maxillary sinuses have been sterile.[2,8]

To our knowledge, this series is the first to report the use of endoscopic sinus surgery for treatment of maxillary sinus atelectasis. This seems to be the most logical approach to the problem, as all patients presented with obvious clinical and radiographic evidence of obstruction of the natural ostium. Kennedy et al[10] achieved a 98% patency rate in 75 patients undergoing endoscopic middle meatus antrostomy for maxillary sinusitis with a follow-up of 4 to 32 months. In treating antral atelectasis, most previous authors have created inferior meatus antrostomies through a Caldwell-Luc approach, a procedure that itself has been reported to have the potential complication of enophthalmos.[3,9] King[11] has shown that mucociliary clearance continues toward the natural ostium after creation of an inferior meatal window. After a Caldwell-Luc procedure, postoperative adhesions could divide the antrum into a number of compartments, further impeding mucociliary clearance. Endoscopic techniques minimize this risk while restoring ostial patency and removing associated anterior ethmoid disease. In this series, we have chosen to address the residual orbital and malar deformities at a second procedure, once there has been resolution of progressive antral collapse and enophthalmos, should the patient find this cosmetically or functionally necessary.

It is striking that 3 patients should present with this rarely reported complication of maxillary sinus hypoventilation over a 2-month period. Cline and Rootman[4] reported that 26 cases (4%) of enophthalmos were diagnosed from a pool of 756 patients referred to their orbital clinic over a 5-year period. Of these 26 cases, 2 (8%) were found to be secondary to maxillary mucocele. Albeit rare, maxillary atelectasis with enophthalmos is an important complication of maxillary sinusitis, and treatment requires close cooperation between the ophthalmologist and the head and neck surgeon.

CONCLUSIONS

We have reviewed three cases of enophthalmos or cheek depression associated with complete opacification of the maxillary sinus. All cases had radiographic and endoscopic evidence of obstruction of the osteomeatal complex by a severely lateralized middle turbinate. We speculate that maxillary sinus atelectasis may result from chronic antral hypoventilation secondary to osteomeatal complex obstruction. Recent reports attest to the efficacy of endoscopic surgical techniques for the management of maxillary sinusitis. Endoscopic middle meatus antrostomy may provide for physiologic decompression of maxillary sinus atelectasis while limiting postoperative adhesions within the sinus that could impede mucociliary clearance.

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FOURTH INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON INNER EAR MEDICINE AND SURGERY

The Fourth International Symposium and Workshops on Inner Ear Medicine and Surgery will be held July 17-24, 1994, in Snowmass-Aspen, Colorado. For more information, please contact I. Kaufman Arenberg, MD, Executive Director and Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone (303) 788-4320 or (303) 850-9545; fax (303) 788-4234.

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1993 CONFERENCE ON IMPLANTABLE AUDITORY PROSTHESES

The 1993 Conference on Implantable Auditory Prostheses will be held July 11-15, 1993, on the campus of Bryant College in Smithfield, Rhode Island. This is the sixth in a series of biennial research conferences originating with the 1983 Gordon Conference. The meeting will provide a forum for close interaction among scientists in all disciplines relating to the field of cochlear implants. For further information, contact Chris van den Honert, Division of Otolaryngology–Head & Neck Surgery, Box 3550, Duke University Medical Center, Durham, NC 27710; telephone: (919) 684-6099; E-Mail: chx@dukehrl.mc.duke.edu.

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FAR-ADVANCED OTOSCLEROSIS

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Profound deafness has received increasing attention in recent years, largely because of the availability of cochlear implants. Consequently, it is especially important for otolaryngologists to remember that a "blank" audiogram does not necessarily mean total or even profound deafness. Patients with far-advanced otosclerosis may have no measurable hearing with routine audiometric testing even in the presence of serviceable sensorineural hearing. Review of nine patients (10 ears) who underwent stapedectomy from 1980 to 1987 reveals that seven of the nine (78%), who had been unable to use a hearing aid preoperatively, obtained serviceable hearing with hearing aids following surgery. Otolaryngologists should depend on a good history and tuning fork examination to avoid being misled by the audiogram, and should not hesitate to offer stapes surgery to patients with far-advanced otosclerosis.

KEY WORDS — audiometry, deafness, otosclerosis, stapedectomy.

INTRODUCTION

Postlingually deafened patients who do not receive adequate benefit from hearing aids are seeking medical evaluation with increasing frequency. Cochlear implants are largely responsible for the recent attention to profound deafness. Although profound sensorineural hearing loss may produce a "blank" audiogram with no response at any frequency, it is important to remember that a blank audiogram does not necessarily mean absence of hearing. Sheehy[1] pointed out that patients with far-advanced otosclerosis (FAO) may also present with this audiological profile. A blank audiogram may only mean that hearing is beyond the measurement limits of the audiometer. For bone conduction, at most frequencies this is around 60 dB hearing threshold level (HTL). For air conduction, it is around 110 dB hearing level (HL). Bone conduction readings may also be falsely depressed in the presence of stapes fixation (Carhart's notch, for example). Consequently, a patient with a 65-dB bone conduction level and a 60-dB air-bone gap would probably have a blank audiogram suggesting total deafness. Such a patient would also have great difficulty functioning even with a powerful hearing aid. Yet, an easily aidable 65 dB HL may be achieved following stapedectomy.

Far-advanced otosclerosis generally involves air conduction levels worse than 85 dB HTL, and bone conduction levels beyond the limits of the audiometer. If air conduction levels exceed 85 dB HTL, but bone conduction levels are measurable at some frequencies but worse than 30 dB, the condition is called advanced otosclerosis. Far-advanced otosclerosis may be suspected because of clues in the history and physical examination, but definitive diagnosis requires middle ear surgery. It is not feasible to use the usual criterion (closure of air-bone gap) for assessing the results of surgery; other objective and subjective criteria should be used.

PATIENTS AND METHODS

Nine patients (10 ears) with unserviceable hearing from otosclerosis underwent stapedectomies performed by one surgeon (R.T.S.) from 1980 through 1987. All patients had air conduction levels exceeding 85 dB HTL in the speech frequencies. Six patients had no measurable bone conduction. Three patients were included who had measurable bone conduction at some frequencies, but who had unmeasurable word discrimination ability and were unable to benefit from amplification (cases 7, 8, and 9). Although these cases were, technically, advanced otosclerosis rather than FAO, the specific patients included were clinically indistinguishable from the other patients. The age range of patients was 50 to 88 years (mean age 73 years), and the male to female ratio was 2:7. Review of two cases illustrates typical findings and results, and information about all cases is summarized in Table 1.

Case 1. A woman, 88 years old at the time of the evaluation, had developed progressive hearing loss in childhood and had become severely hard of hearing in her 20s. She had been able to function with body aids until approximately 1 year prior to evaluation, when her hearing seemed to deteriorate further. She was still active as an internationally famous artist and was profoundly disturbed by her recent inability to communicate. She had no tinnitus or vertigo, but her communication problems were compounded by bilateral macular degeneration. An audiogram re-

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TABLE 1. PATIENT SUMMARY

Case No.	*Preop PTA (dB HTL)*	*Postop PTA (dB HTL)*	*Preop Dis-crim (%)*	*Postop Dis-crim (%)*	*Patient Satis-faction*
1	NR	95	DNT	12	Yes
2	NR	100	DNT	90*	Yes
3	NR	67	0	56	Yes
4	NR	92	0	0	Yes
5	R NR	75	0	60	Yes
	L NR	77	0	0	
6	102	67	0	0	Yes
7	100	NR	0	0	No
8	98	75	DNT	DNT	No
9	NR	72	0	0	Yes

PTA — pure tone audiometry, HTL — hearing threshold level, NR — no response, DNT — did not test.

* Aided word discrimination in sound field.

vealed hearing levels greater than 100 dB in the speech frequencies bilaterally, with no response at several frequencies, and no response by bone conduction. She was unable to hear a tuning fork placed against her mastoid, but was able to hear it well when it was placed against her teeth. Her Weber test was midline, and dental bone conduction was much better than air conduction bilaterally. When the 512-Hz tuning fork was placed against her teeth, the patient was able to hum the pitch "C," confirming that she was *hearing* the tuning fork, not simply feeling it. With Barany masking in her left ear, she was able to hear and understand a loud shouted voice in her right ear. Following uncomplicated right stapedectomy, her pure tone responses improved substantially (Table 2). Word discrimination ability improved from 0% to 56% correct. A sound field speech reception threshold was obtained at 40 dB HL with an aid fitted to the right ear. She was able to use a behind-the-ear hearing aid without difficulty and resume her normal activities.

Case 2. A woman, 74 years old at the time of examination, had been aware of her hearing loss and tinnitus since age 13 years and had a family history of otosclerosis. She still used a body aid on the left ear with more success than one would predict from her audiogram, but she had substantial difficulty hearing even with amplification. With the 512-Hz tuning fork on her teeth, her Weber test was midline, and bone conduction was greater than air conduction bilaterally. With Barany masking in her left ear, she was able to hear a loud shouted voice in her right ear. Her audiogram showed no measurable responses by bone conduction, and no response by air conduction except at 90 dB at 250 Hz in the left ear. She underwent right stapedectomy in October 1985, and left stapedectomy in August 1986. Following surgery, her air conduction responses improved substantially (Table 3), bone conduction became measurable at two frequencies, and her discrimination improved from 0% to 60% in the right ear. She became able to use a hearing aid successfully in her right ear, and felt comfortable resuming social activities she had abandoned because of her hearing loss, particularly traveling and ballroom dancing.

RESULTS

The success of stapedectomy in treating FAO is determined by objective and subjective criteria. Objective improvement may be noted in pure tone thresholds under earphones and in a sound field, in word discrimination ability, and in hearing aid performance. Subjective patient satisfaction with amplification is the real measure of success, however.

The results seen in nine patients (10 ears) are summarized in Table 1. Preoperatively, none of our patients were successful hearing aid users, although several of them continued to wear hearing aids anyway. Postoperatively, seven of the nine patients (78%) used hearing aids successfully. Patient satisfaction following surgery could not always be predicted by word discrimination ability for pure tone responses. For example, in case 8 the patient was not satisfied despite improvement in pure tone threshold from 98 dB to 75 dB. We classified this patient as one of our two failures. If we had used only objective audiometric criteria, as did previous authors, the success rate would have been 89%, since eight of the nine patients had improved thresholds. Interestingly, two of the three patients with measurable bone conduction were not able to benefit from amplification postoperatively.

TABLE 2. AUDIOMETRIC RESULTS IN DECIBELS FOR CASE 1

		Right Ear (Hz)						*Left Ear (Hz)*					
Date	*Conduction*	*250*	*500*	*1,000*	*2,000*	*4,000*	*8,000*	*250*	*500*	*1,000*	*2,000*	*4,000*	*8,000*
8/81 (preop)	Air	NR	100	100	NR	NR	NR	90	100	100	100	95	NR
5/84 (postop)		70	70	80	85	90	NR	NR	105	100	100	95	NR
8/81 (preop)	Bone	NR	NR	NR	NR	NR		NR	NR	NR	NR	NR	
5/84 (postop)		45	55	70	NR	NR		NR	NR	NR	NR	NR	

Speech reception on 5/84 was 40 dB hearing threshold level (aided in sound field). Speech discrimination was 0% right and left on 8/81, and 56% right and 0% left on 5/84.

NR — no response.

TABLE 3. AUDIOMETRIC RESULTS IN DECIBELS FOR CASE 2

		Right Ear (Hz)						*Left Ear (Hz)*					
Date	*Conduction*	*250*	*500*	*1,000*	*2,000*	*4,000*	*8,000*	*250*	*500*	*1,000*	*2,000*	*4,000*	*8,000*
7/85 (preop)	Air	NR	NR	NR	NR	NR	NR	90	NR	NR	NR	NR	NR
3/86 (postop)		70	70	30	75	75	NR						
10/86 (postop)								45	75	70	85	90	NR
7/85 (preop)	Bone	NR	NR	NR	NR	NR		NR	NR	NR	NR	NR	

Speech discrimination on 7/85 was 0% right and left; on 10/86 it was 60% right and 0% left.
NR — no response.

DISCUSSION

Despite 125 cases of FAO discussed in reports written over more than 30 years (Table 4[2-8]), the relationship of severe or profound cochlear hearing loss and otosclerosis is poorly understood. Histologically, the correlation between bone disease and perceptive loss remains obscure in most temporal bones described to date. Lindsay and Hemenway[9] describe two types of otosclerosis. Type 1 is usually a conductive disturbance limited to specific areas of the oval and round windows. The second type of otosclerosis is a more aggressive form with multiple foci that form early in life. These foci involve multiple areas in the otic capsule.

Wiet et al[7] studied the temporal bone of a 65-year-old patient with FAO who died of natural causes. There were multiple foci of otosclerosis, diffuse loss of hair cells, and loss of cochlear neurons in the basal turn. There were also areas of strial atrophy near the foci of otosclerosis. Myers and Myers[10] examined the temporal bone of a 66-year-old man who died suddenly several hours after his second stapes operation for FAO. They found atrophy of the spiral ligament with basilar membrane rupture and severe degeneration of the organ of Corti, spiral ganglion cells, and cochlea.

A convincing histologic explanation for the increased bone conduction threshold in FAO remains an issue for continued investigation. In a total of 164 temporal bones examined by Schuknecht and Barber,[11] a statistical analysis failed to show any correlation between bone conduction thresholds and size of lesion, activity of lesion, involvement of the endosteum, or presence of a round window lesion.

It is presumed that otosclerotic involvement of the cochlear endosteum causes atrophy of the spiral ligament. Basilar membrane rupture appears related to this atrophy, as two of the layers of the basilar membrane insert into the endosteum. How this is related to sensorineural hearing loss remains uncertain. Otosclerosis may cause atrophic changes leading to alterations of the motion mechanics in the scala media; mechanical and metabolic alterations due to strial atrophy may be causal; or some other mechanism may be responsible for the sensorineural loss.

Clinically, it is extremely important to recognize FAO. Wiet et al[7] diagnosed three cases of FAO among 175 patients who were being considered for cochlear implantation. Two of these patients underwent stapedectomy and received substantial benefit from hearing aids following surgery. Stapedectomy involves much less risk than cochlear implantation, and less rehabilitation. Moreover, the hearing achieved with amplification following stapedectomy is generally better than the hearing expected with a cochlear implant. When satisfactory results are not achieved, the patient may still be considered for cochlear implant surgery.

When a patient presents with acquired severe or profound hearing loss, a comprehensive neurologic evaluation is mandatory to diagnose causes such as neoplasms, luetic labyrinthitis, autoimmune sensorineural hearing loss, ototoxicity, meningitis, and genetic hearing loss. However, since FAO is one of the few conditions that permits treatment capable of converting the patient's hearing from nonserviceable to serviceable with conventional hearing aids, it is especially important to be alert for this entity, and to look for residual, nonmeasurable hearing and an air-bone gap. The definitive diagnosis requires middle ear exploration. However, Sheehy[5] summarized the symptoms and signs that are generally regarded as most typical of FAO, and that should alert the otologist to the possible presence of this entity. They include the following.

History. Gradually progressive hearing impairment in early adult life is suggestive, especially with a positive family history of otosclerosis. Eighty-six percent of Sheehy's[5] patients who had onset of hearing impairment before age 30 years and a positive family history had oval window otosclerosis.

Paracusis. The ability to hear better in noisy surroundings during an early stage of hearing impairment is highly suggestive of otosclerosis.

Hearing Aid Performance. Despite the extent of the hearing loss, patients report some benefit from amplification. Word discrimination ability without

TABLE 4. LITERATURE REVIEW

Authors	*Year*	*Diagnoses of Far-Advanced Otosclerosis*
House[2]	1959	4
Willis[3]	1963	28
Myers et al[4]	1963	20 (26 ears)
Sheehy[5]	1964	46 (67 ears)
Sellars[6]	1972	10
Wiet et al[7]	1987	2
Babighian et al[8]	1991	15
This study		9 (10 ears)

lipreading is better than would be predicted on the basis of pure tone thresholds. Eighty percent of patients with FAO wore hearing aids, as opposed to only 30% of patients with nonotosclerotic ears who had similar audiograms in Sheehy's series.[5]

Hearing Aid History. The patient may be wearing or in the past was wearing a hearing aid or bone conduction aid.

Previous Audiograms. A prior audiogram may demonstrate an air-bone gap.

Voice Patterning. The voice may not be suggestive of sensorineural hearing loss (modulation, pronunciation, and intensity).

Otoscopic Examination. Schwartze's sign may be present.

Radiographic Confirmation. Although polytomography may further support the diagnosis of FAO, preoperative confirmation with computed tomography (with coronal views) is especially helpful. Von Glass and Philipp[12] investigated 31 patients suspected of having cochlear otosclerosis with high-resolution computed tomography. Fourteen patients had confirmed otosclerosis associated with advanced hearing loss. In 4 of these patients, fresh otospongiotic foci were detected in the bone of the cochlear capsule.

Tuning Fork Testing. A Weber test lateralizing to the poor ear or a negative Rinne test in presumed sensorineural hearing loss may be suggestive. Because of tactile perception, tuning fork tests may sometimes be misleading. We recommend standard use of a 512-Hz tuning fork. Many patients with FAO do not hear the tuning fork well when it is placed on the forehead or nasal dorsum, but hear clearly by dental bone conduction. In order to help confirm the validity of tuning fork testing, in 1980 one of the authors (R.T.S.) began asking patients to hum the pitch of the tuning fork. This is a simple task for people with even extremely modest musical ability. All of our patients with FAO were able to perform this task. None of our patients with profound sensorineural hearing loss who subsequently went on to cochlear implant surgery was able to perform the task.

No Other Apparent Cause for Hearing Impairment. When hearing loss has been of insidious onset, and when all other known causes have been ruled out, the diagnosis of FAO must be considered, especially if any of the criteria listed above are present.

The value of surgery for this disease entity was first discussed in 1960 by House and Glorig.[13] Surgical improvements are much more important to a patient with FAO than to a patient with a mild to moderate hearing loss, because surgery can convert FAO patients from functionally deaf to easily aidable. House and Glorig were two of many investigators to conclude that opening the oval window in patients with FAO was potentially worthwhile regardless of the level of preoperative air and bone conduction thresholds. This philosophy still prevails some 30 years later.

The reported surgical experience is summarized in Table 5.[2-8] Our results support the findings of the three previous reports with the best results.[2,3,6] The type of prosthesis and surgical technique used, and involvement of the round window by otosclerosis, appear to have no bearing on the success of surgery. House and Glorig[13] opened both windows in a two-stage operation. In three of five patients, the hearing was made worse. The round window should generally not be opened for this reason, and because closure of the round window probably accounts for only 10 dB of bone conduction loss at most.[13]

For routine cases of otosclerosis, we generally define surgical success as closure of the air-bone gap to within 10 dB. In experienced hands, we expect a success rate above 90%. On the basis of these conventional criteria for stapedectomy surgery, results in FAO would be disappointing. However, the majority of patients with FAO clearly benefit from stapedectomy subjectively, and many have improvements in pure tone air conduction thresholds. Some also have improvement in discrimination ability under earphones; and marked improvement in hearing aid performance is common. Patients are often able to use their amplified hearing more effectively, even when the traditional measures of discrimination do not show improvement. Careful preoperative counseling and informed consent are extremely important in patients with FAO. The patients must be aware not only of the risks of the procedure, but also of the relatively limited goals. Normal hearing is not expected. Reported complications in these patients do not appear to differ statistically from those in other patients undergoing stapedectomy surgery; and most

TABLE 5. RESULTS OF SURGERY

Authors	*Year*	*Hearing Improved*	*No Change*	*Worse*	*Overall Success*
House[2]	1959	3	1	0	75%
Willis[3]	1963	21			75%
Myers et al[4]	1963	14	9	3	54%
Sheehy[5]	1964				46%
Sellars[6]	1972	8	2		80%
Wiet et al[7]	1987	2			2/2
Babighian et al[8]	1991	8	5	2	53%
This study		8	0	1	89%*

*By audiometric criteria, as reported by previous authors. By subjective criteria, results are 7 of 9 patients, or 78% improvement.

patients feel justified in accepting those risks for the potential benefit of advancing from unserviceable hearing to aidable hearing.

Controversy exists as to whether a second stapedectomy for FAO should be performed on the opposite ear. Many otologists believe that there is little justification for this in the event of a successful stapedectomy. We believe, however, that each case should be addressed individually, that each patient should be offered the potential benefit of binaural amplification even for a hearing loss of this severity, and that the final decision should be left to the patient after the risks have been explained fully.

If an operation for FAO has failed, many investigators suggest that an attempt at surgery on the opposite ear would also probably fail, and that further surgery is not advisable. We question this anecdotal judgment and believe that the decision regarding surgery on the opposite ear should be individualized in this instance, as well. When hearing loss is profound bilaterally, the patient assumes very little risk from undergoing stapes surgery; and results may be substantially different on the two ears, as illustrated by discrimination scores in our case 5 (Table 1).

CONCLUSIONS

Despite technologic advances, FAO remains difficult to diagnose. Because failure to recognize the condition may result in a lack of treatment or unnecessary cochlear implant surgery, otolaryngologists must be cognizant of this entity. Careful history and physical examination usually suggest the diagnosis. Tuning fork testing should be performed in all patients with audiometrically unmeasurable hearing. Loud spoken voice testing with Barany masking may also be helpful. When FAO is diagnosed, the potential benefits of surgery appear to justify the risks, even in patients of advanced age. Conversion from unserviceable to serviceable aided hearing is a worthwhile therapeutic goal that can result in a most gratifying improvement in a patient's quality of life.

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GUSTATORY OTORRHEA: FREY'S SYNDROME OF THE EXTERNAL AUDITORY CANAL

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A case of Frey's syndrome of the external auditory canal is reported. The patient presented with unilateral gustatory otorrhea and thickened external auditory canal skin. Histopathologic examination of the canal skin showed sudomotor gland hyperplasia. Symptoms were relieved with canal skin excision and skin graft.

KEY WORDS — **auriculotemporal syndrome, ear canal, external auditory canal, Frey's syndrome, gustatory sweating.**

INTRODUCTION

Frey's syndrome is named after Lucie Frey's 1923 case report and discussion of gustatory sweating.[1] The author reported a 25-year-old soldier who had suffered injury to the angle of the mandible and the left side of the face, and who sweated and flushed with eating. It was speculated that this patient's symptoms were caused by aberrant reinnervation of skin adnexal structures by autonomic fibers of the 9th cranial nerve, which had been disrupted by the trauma.

Although this syndrome affects many areas of the head and neck and follows a variety of traumas,[2-5] there is no report of Frey's syndrome affecting the external auditory canal. We present here such a case, and include a histologic specimen that illustrates the syndrome well.

CASE REPORT

For 6 months, a 36-year-old woman had noted watery otorrhea from the left ear only with eating. There was no preceding history of trauma or infection to the auricular area. Initially taken to be otitis externa, this condition was treated with antibiotics. When her otorrhea failed to abate, she was referred to us.

On physical examination clear fluid welled up in the inferior lateral external auditory canal. A fistula from the parotid gland to the external auditory canal was hypothesized. A temporalis fascia graft, placed between the external canal skin and parotid gland, failed to alleviate the symptoms.

The canal was carefully reexamined over many minutes, with use of suction and blow-drying followed by gustatory stimulation. There were discovered multiple pinpoint excretions of fluid over the entire skin of the membranous canal. The fluid was thus sweat and not saliva. The diagnosis of Frey's syndrome was then made. The entire external auditory canal skin was removed at the next operation, and a split thickness skin graft was used to replace the membranous canal skin. Thereafter the patient no longer experienced otorrhea, even when eating spicy

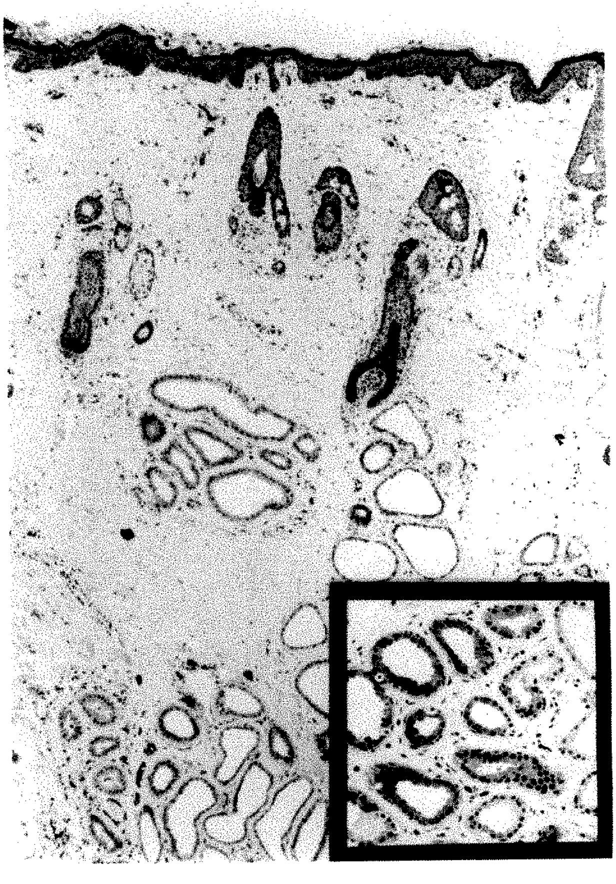

Fig 1. Skin of affected external auditory canal (H & E, original x35). Canal skin is 4.2 mm thick throughout its entire length, and shows hyperplasia of adnexal sweat glands. Inset) Original x70.

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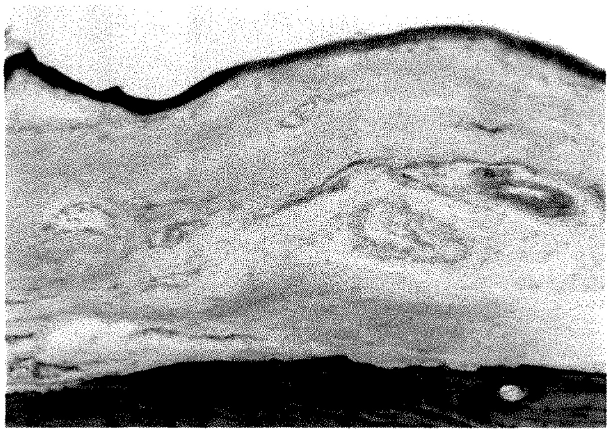

Fig 2. Skin of normal bony external auditory canal (H & E, original x750). Thickness is 0.08 mm. Skin of this thickness covers most of bony canal, and is devoid of most glandular structures.

foods.

Histopathologic examination showed markedly thickened ear canal skin and greatly hypertrophic subcutaneous sweat glands (Fig 1).

DISCUSSION

We report the first case of Frey's syndrome involving the external auditory canal. Several features of this case made the diagnosis particularly difficult. The history of intermittent otorrhea was easily taken for an infection of the external canal. Since Frey's syndrome involving the external canal had not been reported before, the diagnosis was difficult to deduce. Indeed, the more likely possibility of a fistula from the parotid to the external canal was explored first. Finally, even had Frey's syndrome been suspected initially, the absence of any history of trauma or infection would have militated against this diagnosis.

Particularly interesting here is the availability of biopsy material for analysis and diagnosis. The normal external auditory canal skin is thin, closely applied to the periosteum, and shows adnexal features interspersed among the fibrous tissue of the dermis (Figs 2 and 3). In this patient, the skin of the entire length of the external canal is more than four times the normal thickness, and is dominated by hypertrophic sweat glands, which do not normally exist in bony canal skin, and here is abnormally proliferated into bony canal skin, presumably by parasympathetic autonomic influence (Fig 1). This remarkable glandular hyperplasia appears to be the effect of abnormal sympathetic stimulation to the canal skin and, along with the history, confirms the diagnosis of Frey's syndrome.

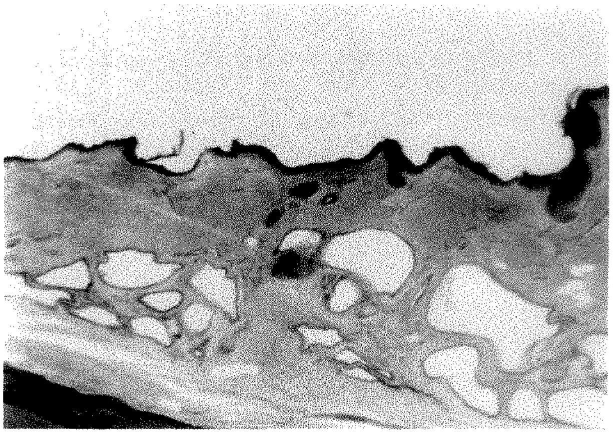

Fig 3. Skin of normal cartilaginous external auditory canal (H & E, original x60). Thickness is 0.85 mm. This skin is thicker than skin of bony canal and demonstrates more prominent glands, but is thinner than skin shown in Fig 1 and, unlike that skin, does not cover entire external canal.

Frey's syndrome results from the misdirection of parasympathetic fibers of the 9th cranial nerve to skin appendages.[1,3-5] Trauma or infection is thought to disrupt the neuronal pathways, leaving the severed axons free to regrow aberrantly. The anatomy of the misdirection of parasympathetic fibers has been outlined in the case of gustatory sweating after parotidectomy or parotitis.[1-4] Postganglionic parasympathetic and sympathetic fibers travel together on the auriculotemporal nerve. When these postganglionic fibers are disrupted, the parasympathetic fibers can regrow along the routes of the cervical sympathetic nerves to innervate the sweat glands and vessels of the facial skin. As a result, the parasympathetic impulse of salivation causes the sympathetic responses of sweating and vasodilation.

The middle ear, too, contains several adjacent neuronal pathways.[6] Branches of the 7th, 9th, and 10th cranial nerves leave the middle ear to provide sensation as well as sudomotor innervation to the external auditory canal. Within the middle ear space are parasympathetic fibers to the salivary glands. They are fibers of the 9th nerve, coursing across the promontory en route to the parotid, parasympathetic fibers of the 7th nerve contained in the chorda tympani en route to the submandibular gland, and occasionally parasympathetic fibers of the 9th nerve traveling in the chorda tympani en route to the parotid. Crossover between these sudomotor and parasympathetic fibers is presumably the cause of the Frey's syndrome seen in this patient, although no disruptive incident was found by history or physical examination.

In summary, we present a rare case of Frey's syndrome involving the external auditory canal and presenting with gustatory otorrhea. Histologic examination of the affected skin confirms the diagnosis.

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SAN FRANCISCO OTOLOGY UPDATE — 1993

A comprehensive review of contemporary otology and neurotology is offered for the practicing otolaryngologist or resident in training. It will be held at the Ritz-Carlton Hotel, San Francisco, California, on November 4-6, 1993. For further information, contact UCSF Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; phone (415) 476-4251.

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HHT CONFERENCE

The Second Annual Conference of the HHT Foundation International, Inc, will be held in San Francisco, California, on June 19-20, 1993, at the Sir Francis Drake Hotel. The purpose of the foundation is to provide information and support to patients and families with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). For more information, contact Rita VanBergeijk, HHT Foundation President, PO Box 8087, New Haven, CT 06530; (313) 561-2537.

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AIRWAY COMPLICATIONS IN THYROID SURGERY

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Perioperative and postoperative morbidity and mortality were studied in a series of 3,008 thyroidectomies. Compressive symptoms, frequent in substernal and cancerous goiters, were present in 11.0% of the patients, although a low rate of dyspnea (2.7%) was observed. In large goiters, some orotracheal intubations were difficult. In such cases, the transtracheal approach can also be difficult, so failure should be anticipated. Postoperative causes of respiratory obstruction included local hemorrhages, bilateral recurrent nerve palsies, and laryngeal edema. A tracheal collapse was not observed. These respiratory obstructions led to repeat surgery in 11 patients, tracheostomy in 3, and temporary reintubation with steroid therapy in 1. The recurrent laryngeal nerve, which may have been affected preoperatively, was found to be damaged postoperatively in 0.5% of the patients with benign goiters, compared to 10.6% of the patients with thyroid cancer. In this last group a bilateral palsy was observed in 3 cases with prolonged or extensive surgery. After these short-term orotracheal intubations (114 minutes on average), injuries of the airway caused by the endotracheal tube were found in 4.6% of the patients.

KEY WORDS — complications, hemorrhage, laryngeal nerve, short-term intubation, thyroidectomy.

Postoperative complications of thyroidectomy usually consist of local hemorrhage and/or unilateral recurrent laryngeal nerve (RLN) palsy. The frequency of these palsies recorded in the literature varies widely (0% to 37.3%).[1,2] We report here on these complications for 3,008 thyroidectomies performed over a 20-year period at Jean Bernard Hospital. The problem of RLN palsy is discussed and is treated in the more general context of throat complications of goiters and thyroidectomies. The series is to date the largest to have been controlled systematically with postoperative laryngoscopy. This is a useful tool for evaluating not only the surgical complications of thyroidectomy, but also the laryngeal injuries caused by the tubes after short-term tracheal intubation.

PATIENTS AND METHODS

The medical charts of 3,008 patients who underwent thyroid surgery between 1968 and 1988 were reviewed. Information was collected on the following: compressive signs, intubation, tracheostomy, hemorrhage, RLN complications, throat-related death, and local laryngeal trauma caused by tracheal tubes.

The patients had a mean age of 45 years (range 8 to 87 years) and a female to male ratio of 7:3. The types of surgical procedures performed are listed in Table 1. In this series, thyroidectomy was performed for benign nodules (80%), warm nodules or toxic disease (14%), and malignant tumor (6%). Surgery for recurrence represented 2.5% of the total patients. Most patients (88%) underwent unilateral or subtotal thyroidectomy. General anesthesia was chosen for all patients, with the use of flexible armored tube (Rush) for the orotracheal intubation. The patient's head was placed in the hyperextension position, and respiration was controlled in all cases. A nasogastric tube was inserted in patients with large compressive goiters or with substernal goiters to help guide the dissection. After surgery, on day 3 or day 5, the otolaryngology team performed an indirect laryngoscopic examination on all patients. The average (±SD) duration of the tracheal intubation was 114 ± 31 minutes.

RESULTS

The patients had been referred for exploration of a cervical mass (52%), changes in a known goiter (24%), compressive symptoms (5.5%), or cervical adenopathies (0.76%). Pain was rarely reported (0.13%). Compressions involved the digestive tract (91 cases), the respiratory tract (44 cases), the RLN (27 cases), or the vascular trunk (6 cases).

TABLE 1. TYPES OF SURGICAL PROCEDURES

	Benign Goiter (n = 2,829)	*Cancer (n = 179)*
Unilateral surgery	54%	24%
Bilateral surgery	46%	43%
Extended surgery		33%

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TABLE 2. RECURRENT LARYNGEAL NERVE PALSY FOUND ON POSTOPERATIVE LARYNGOSCOPY

	Temporary Palsy (% of operations)	*Permanent Palsy (% of operations)*
Benign goiters	4.4	0.5
Graves' disease	1.7	
Substernal goiters	8.0	4.0
Cancers	2.2	10.6
Total (3,008 cases)	4.3	1.1

On preoperative examination, clinical compressive symptoms were indeed detected in 11% of the cases, including 2.7% with dyspnea. Anteroposterior chest and cervical radiographs showed tracheal changes in 800 cases; of that group 219 had moderate deviations with one tracheal surface deviated lateral to the cervical spine, 307 had the entire trachea thus deviated, and 105 had a narrowed trachea.

Preoperative laryngoscopy in selected patients with benign goiter identified RLN paresis (n = 2) and unilateral RLN palsy (n = 7). Unilateral nerve palsy was found in 8 patients of the 179 with thyroid cancer.

In 6% of the tracheal intubations, the tube was inserted after a spray of local anesthetic with the patient breathing spontaneously, because a difficult intubation was expected from the preoperative examination. One intubation was impossible, and three were reported as very difficult, including the use of fiberoptic endoscopy once.

Because of local hemorrhage a second operation was necessary in 11 patients, some of whom had compression hematoma. Four patients were then monitored postoperatively in the intensive care unit.

Intraoperative dissection exposed the RLN in 2,427 patients, during which a nonrecurrent laryngeal nerve was recognized in 2 patients.[3] After operation, laryngoscopy revealed a temporary nerve palsy in 130 patients (4.32%), a permanent palsy in 34 patients (1.13%), and other otolaryngological lesions in 138 patients (4.6%). The results of RLN examination are given in Table 2. Injury or risk of injury to the RLN indicated postoperative monitoring in the intensive care unit for 10 patients. Seven of them had a thyroid neoplasm. In 3 patients with postoperative bilateral RLN palsy a tracheostomy was needed. In the perioperative course tracheostomy was actually required in 11 patients (0.36%). The other eight tracheostomies were performed on patients with extensive thyroid cancer to palliate end stage disease. One patient required two tracheostomies: the first was performed for a bilateral RLN palsy and was followed by an endoscopic laser arytenoidectomy; the second was performed for respiratory obstruction caused by tumor recurrence.

Sixteen deaths occurred during the first 30 postoperative days. They were related to extensive cancers (five cases), cardiovascular disorders (five cases), and respiratory complications (six cases). In this last group four deaths were related to some otolaryngic dysfunction. The first death occurred following a tracheal intubation failure with pulmonary aspiration of gastric contents. The patient had an extremely large malignant goiter with a deviated and constricted trachea. Another death was a direct consequence of a difficult tracheostomy with ensuing cerebral anoxia. The third death was due to a respiratory failure on postoperative day 3 after a difficult extubation on day 1. The patient was a 64-year-old woman who underwent thyroidectomy for a 1,216-g benign goiter. She had vomited heavily the night before her death. A glottic dysfunction with RLN injury was suspected. The surgical control of the RLN had been impossible during the removal of this giant benign asphyxic goiter. The fourth death occurred in a 66-year-old man with chronic renal failure and postoperative pulmonary infection. Laryngoscopy on day 6 (2 days after extubation) showed the vocal cords in a paramedian position without abduction during inspiration. This bilateral RLN injury was probably responsible for gastric aspiration or ineffective cough, leading to a pulmonary infection that in turn worsened the renal failure.[4]

DISCUSSION

Preoperative Complications. The symptoms resulting from the enlargement of the thyroid gland represent the most frequent initial symptoms for this cervical condition. Compressive signs were the initial symptoms in 5.5% of the cases in the overall series, 17% of the cancer cases, and 21% of the substernal goiters. Given the clinical discomfort, it is surprising that half of the patients with compressive symptoms initially should consult for another symptom (cervical nodule, swollen neck, etc). The progressive character of the growth of thyroid nodules may explain the tolerance for and neglect of these alarming symptoms by the patients.

In our series dyspnea, dysphonia, dysphagia, or venous obstruction was present in 330 cases. This incidence is 2.5 times higher than the 4.5% incidence reported in 1,000 patients by Mellière et al.[5]

Compression by an enlarged thyroid gland on the trachea is very common, as displayed on 26% of the preoperative chest and cervical radiographs in our patients. In series by Lundgren and Heimann[6] and by Blomstedt,[7] prevalences of 16.5% and 45% were reported for tracheal compression or displacement. Among our patients with marked tracheal deviation and those with tracheal compression, only 2.7% presented with dyspnea. This is similar to the frequency observed by Lange[8] in a population of 3,500 goiters submitted to surgery.

Mirror examination of the larynx was performed before operation when an RLN lesion was suspected, ie, in goiters with dysphonia and in cases of previous partial thyroidectomy. However, it was not a routine examination. Dysphonia was observed in 96 patients. Among them, 22 had a laryngeal examination before surgery; we found only 8 palsies and 2 pareses of the RLN. Thus, dysphonia is not always a sign of RLN palsy or paresis. Some dysphonias stem from a mechanical dysfunction caused by the thyroid enlargement and its relationship to the vocal structures of the larynx and trachea. For the whole group, unilateral palsies were observed in 7 patients with benign goiters and in 8 with cancer. Therefore, RLN palsy is not a good predictor of malignancy in patients with goiter. It would be advisable to examine all patients before surgery to detect possible asymptomatic RLN palsy, which can coexist with a fairly good voice.

Finally, vascular compression symptoms caused by an enlarged thyroid gland are rare. In our series, they were observed in six patients with partial obstruction of the superior vena cava.

Perioperative Complications. When a goiter involves the airway, it can lead to a difficult tracheal intubation. We were confronted with four such very difficult cases in this series. There may be limited exposure of the glottic area or difficult glottic or tracheal catheterization by the tube. In that case, the emergency transcricothyroid membrane or transtracheal procedure may be impossible or difficult because of an enlarged thyroid gland. One needs to be ready, if necessary, to use other techniques such as fiberoptic endoscopy. A difficult tracheal intubation may also occur when a patient is naturally difficult to intubate. Factors predictive of difficulty in inserting a tracheal tube have been studied in the general population, but they remain to be investigated in the population with surgical goiters.

Postoperative Complications. After surgery, causes of respiratory obstruction included local hemorrhage, bilateral RLN palsy, and laryngeal edema. Airway obstruction should be distinguished from the central depression induced by anesthetic drugs, especially narcotics.

In our series, local hemorrhages or hematoma occurred in 0.36% of the cases and made repeat surgery necessary. Similar frequencies (0.1% to 1.1%) were reported in the literature for this complication (Table 3[1,8-14]). Some hemorrhages occurred from 5 minutes to 3 days after the initial surgery. However, a reexploration of the neck was required 24 hours after the operation in only two cases. Thus, these hemorrhages are rare. However, careful monitoring of the patient by the nursing staff is needed to avoid long-lasting bleeding that could block the airway.[7] In the case of an acute asphyxia, tracheal intubation is of paramount importance. The reopening of the surgical wound is rarely indicated to make the tracheal intubation easier. It may be helpful to use a small-diameter tracheal tube, as laryngeal edema is often present.[15] Among patients with thyroid cancer, bilateral RLN palsy occurred three times. In these three cases, the vocal cords were in adduction and a tracheostomy was necessary to control the airway. The second reason to perform tracheostomy was the respiratory rescue of the patients with extensive cancer. (In that case, the survival was very short: 3 months or less.) The frequency of tracheostomy is reported to vary from 0% to 1.66%[1,8-14] (Table 3). One patient with laryngeal respiratory distress had subglottic edema as evidenced by the laryngoscopic control examination.[15-17] The patient was extubated on day 5 after a course of steroid therapy. Another cause of respiratory failure is described in the literature as tracheal inspiratory collapse.[18] It is caused by softening of the tracheal rings and the loss of support from the surrounding goiter. This complication was not observed in our series.

TABLE 3. POSTOPERATIVE TRACHEOSTOMY AND HEMATOMA

Authors	*Year*	*No. of Operations*	*Tracheostomy (%)*	*Hematoma (%)*
Cattell and Morgan[9]	1939	4,956	0.10	0.50
Beahrs et al[10]	1956	1,021	1.66	0.19
Yovanovitch[11]	1960	1,500	0.06	0.26
Lange[8]	1961	3,500	0.03	0.37
Mandl[12]	1965	2,200	0.45	0.45
Gould et al[13]	1965	1,000	0.50	1.10
Foster[14]	1978	24,108	0.51	0.66
Karlan et al[1]	1984	1,000	0	0.10

The RLN is particularly subject to injury during surgery on the thyroid gland. An indirect laryngoscopy was therefore carried out 3 to 5 days after surgery by the otolaryngology team and repeated when abnormalities were noticed. The complication rate of RLN palsy was 5.45% based on the number of operations, and 3.77% based on the number of nerves at risk. This includes temporary and permanent, unilateral and bilateral palsies, identified preoperative palsies, and sacrificed nerves. The rate of permanent unilateral RLN palsy for the entire group was 0.99 per 100 operations and 0.67 per 100 nerves at risk.

TABLE 4. INCIDENCE OF VOCAL CORD PALSY IN SERIES WITH POSTOPERATIVE LARYNGOSCOPY

			Unilateral Palsy (% of operations)	
Authors	*Year*	*No. of Operations*	*Temporary*	*Permanent*
Scheicher[19]	1937	1,019	7.00	1.37
Beahrs et al[10]	1956	1,021		2.50
Lundgren and Heimann[6]	1958	1,732	2.54	0.80
Hawe and Lothian[20]	1960	1,011	2.47	0.29
Yovanovitch[11]	1960	1,500	1.13	0.86
Mandl[12]	1965	2,200	0.80	2.00
Riddell[21]	1970	1,700	0.88	1.70
Blondeau et al[22]	1973	1,000	1.30	2.00
Høie et al[2]	1990	1,245*	11.00	21.30

*Cancers.

TABLE 5. INCIDENCE OF VOCAL CORD PALSY IN CASES WITH REOPERATION

Authors	*Year*	*No. of Reoperations*	*Unilateral Palsy (% of operations)*
Scheicher[19]*	1937	311	10.0
Cattell and Morgan[9]*	1939	306	14.7
Troell*	1944	149	14.8
Bertelsen and Becker-Christensen*	1947	39	15.4
Beahrs and Vandertoll[24]	1963	548	11.1
Mandl[12]	1965	180	10.0
Blondeau et al[22]	1973	23	13.0

*Modified from Meurman.[25]

Table 4[2,6,10-12,19-22] presents comparative data for published series exceeding 1,000 patients. All these series were controlled with a postoperative laryngoscopy examination to avoid the frequent underestimation of nerve injuries. In the group of benign goiters, permanent nerve palsies were rare: 0.5 per 100 operations. This low rate should be considered when surgery is proposed to these patients. However, in this group, two deaths may have been related to RLN dysfunction. They underline the necessity for a preventive attitude with an early postoperative laryngeal evaluation and aggressive control of the airway in case of glottic dysfunction. Of interest in the group with benign goiter is the possibility of recovery from preoperative RLN palsies. This occurs in about 30% of cases.[23] The permanent unilateral RLN palsies were more frequent in substernal goiters (4%) and in the cancer group (9%). In substernal goiters, nerve injury was difficult to avoid because of the size of some of these goiters and the resulting anatomic distortion. In the cancer group, 8 unilateral RLN palsies were already present before surgery (4.46%), and 5 were deliberate nerve sacrifices (2.79%). This surgical sacrifice was sometimes necessary because of the invasiveness of these malignant goiters. In this same group, 3 bilateral RLN injuries occurred that required a tracheostomy. Bilateral RLN palsies are rare, but thyroid surgery represents the leading cause of these dramatic injuries in adults.[4] The group with reoperated goiters is associated with an increased risk of permanent palsies: 7%. Similar reports are listed in Table 5.[9,12,19,22,24,25] It is of the utmost importance to examine the larynx of these patients before and after the reoperation. Finally, it should be noted that after thyroidectomy it is impossible to distinguish the very rare nerve palsies caused by the tracheal tube from the more frequent ones caused by dissection injury.[26]

The external branch of the superior laryngeal nerve (ESLN) provides the cricothyroid muscle (tensor for the vocal cords) and the inferior pharyngeal constrictor with motor fibers. Lennquist et al[27] have observed that 20% of ESLNs are highly vulnerable if the superior thyroid artery and its branches are not carefully dissected before division. Injury of the ESLN may occur during thyroidectomy, but the true frequency of these injuries is presently unknown. Injury of the ESLN may also occur in conjunction with an injury of the RLN. These injuries were probably overlooked in our series, as they were in many other series.

Just after surgery, laryngeal edema is often associated with RLN injury to produce airway dysfunction and obstruction.[4,15] This further emphasizes the importance of an immediate postoperative laryngoscopy to detect early any glottic dysfunction. Prolonged intubation or tracheostomy will be necessary in a few patients to enable the edema to subside and the transitory diplegia to recover.

The laryngeal complications of the tracheal tubes are easily studied in these patients; postoperative laryngoscopy allows such an evaluation. Few studies have described the complications resulting from short-term tracheal intubation in thyroid and nonthyroid surgery. In our series, the indirect laryngoscopy performed by the otolaryngology team on day 3 or day 5 after thyroidectomy exposed otolaryngological lesions in 5.15% of the patients, excluding nerve injuries. This frequency is very similar to that reported by Blackburn and Salmon[28] (5.6%). Patients with otolaryngological lesions in our series can be classified into three groups. The first group includes 95 patients (3.16%) with inflammation and edema either of the whole airway from the uvula to the trachea or, more often, in the glottic area (57 patients). Laryngeal edema was more frequent in the series of Martis and Athanassiades[16] (13.5%) and that of Holt et al[17] (13.4%). The timing of the examination and a specific interest in this particular complication may account for the difference. The second group includes 43 patients (1.43%) with more severe trauma. Forty of the traumatized areas were in the glottis (11 hematomas, 11 erosions, 4 ulcers, 3 nodules, and 14 granulomas). The use of a flexible armored tube molding with the anatomic angles of the respiratory tract in a patient with a hyperextended head, neuromuscular block for tracheal intubation and ventilation, and careful surgical manipulations may explain our lower rate of severe lesions compared to the series of Kambič and Radšel[29] (6.2%) and Peppard and Dickens[30] (6.3%). The third group includes 17 patients (0.56%) with miscellaneous lesions (rhinopharyngitis, sinusitis, otitis, polyps). Thus, edema and true traumatic lesions were observed in 4.6% of the patients. The surgical manipulations of the thyroid gland may explain the usual bilaterality of the observed corditis. However, the trauma to the vocal cords was usually posterior. Severe lesions such as deep lacerations, tracheal or esophageal perforations, and arytenoid dislocation were not observed in this series.

The frequent postoperative symptoms of thyroidectomy may conceal symptoms resulting from local trauma as described by Peppard and Dickens[30]: sore throat and odynophagia. Hoarseness is often present before the operation and primarily leads to a suspicion of RLN nerve palsy. Therefore, the postoperative laryngoscopy examination should investigate not only RLN and ESLN injuries, but also local trauma that is not always obvious in this context.

In conclusion, this review of 3,008 thyroidectomies has provided data on the frequency and types of the otolaryngological complications associated with surgical goiters and thyroidectomies. Patients with compressive symptoms usually have substernal goiters or cancers. Half of them do not complain about these compressive symptoms. By and large, 6% of the tracheal intubations in thyroid surgery patients should be expected to be difficult. Since emergency percutaneous procedures are difficult when the thyroid is enlarged, an alternative procedure, such as the fiberoptic method, should be considered when tracheal intubation is not possible. In regard to RLN injuries, two groups of patients can be distinguished: patients with benign conditions, with a frequency of permanent unilateral postoperative palsies of 0.5%, and patients with cancer, with a frequency of postoperative palsies of 10.6%. Repeat surgery for hemorrhage is rare (0.36%). However, the possibility of hemorrhage justifies careful monitoring of patients during the first 24 hours, although hemorrhage can also occur later. Finally, in thyroidectomies, the laryngeal injuries caused by the tracheal tubes are no more frequent (4.6%) than those in other short-term tracheal intubations.

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COCHLEAR WALL TITANIUM IMPLANTS FOR AUDITORY NERVE STIMULATION

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Genetically deaf dalmatian dogs and ototoxically deafened macaque monkeys were implanted with electrodes housed in cochlear wall titanium implants to assess long-term stability, tolerance, and performance. Short-term human implantation, followed by trials of stimulation, was performed in 4 unilaterally deaf patients. In the dog experiments, cochlear wall electrode stimulation produced consistent electrophysiologic thresholds that were higher, by approximately 6 dB, than those obtained with bipolar scala tympani stimulation. Clinical testing revealed electrically evoked middle latency response, auditory brain stem response, and/or behavioral detection responses in 3 of 4 patients, at levels below those for facial nerve activation and pain sensation. Electrode place discrimination studies, with controls for loudness cues, revealed near-perfect discrimination in a monkey subject. Eleven of the 12 animal implants were found to be rigidly fixed in the cochlear bone, with direct contact between bone and implant over 8% to 23% of the implant surface for the 6 implants examined in detail. These results suggest that long-term fixation of titanium cochlear wall implants occurs by virtue of intimate implant-bone contact in restricted areas. This approach to prosthetic stimulation demonstrates encouraging performance characteristics in achieving auditory activation.

KEY WORDS — auditory prosthesis, cochlear implant, cochlear wall, titanium.

INTRODUCTION

The development of methods to electrically stimulate the auditory system in cases of profound deafness has largely centered on the use of electrodes placed within the scala tympani. Intrascalar implantation places electrodes close to auditory neural elements and has demonstrated substantial (re)habilitative benefit with acceptable levels of tissue trauma.

Another approach to prosthetic electrical stimulation is to place electrodes outside the cochlear scala, in the bony wall of the cochlea. The primary impetus for this approach is derived from postulated advantages in reduced trauma to target neural fibers. Implanting the lateral cochlear wall might also provide access to neurons in the middle and apical turns not accessed by standard scalar implants. With many causes of profound deafness, the middle and apical regions contain relatively greater reserves of spiral ganglion cells than does the basal region.[1,2]

An extracochlear strategy of stimulation, however, places electrodes in sites that are more remote from target neurons. Thresholds for activation may be higher, and there is an increased likelihood of stimulating nonauditory structures. The greater distance between stimulating electrodes and nerve fibers may result in stimulation of larger populations of fibers, thereby potentially reducing the place specificity of stimulation.

In an effort to securely anchor electrodes in the cochlear wall, Miller et al[3] and Pfingst et al[4,5] investigated the use of trans–cochlear wall titanium implants. This approach was based on prior observations by Brånemark et al,[6] Albrektsson et al,[7] and Tjellström et al[8] that commercially pure titanium is capable of developing direct contact with bone to achieve firm retention of craniofacial prostheses and bone conduction hearing aids. These prior studies[3-5] have shown that in the absence of infection, titanium cochlear wall implants achieve a high rate of stability, although excessive length of the implant shaft can produce a fibro-osseous reaction within the scalae.

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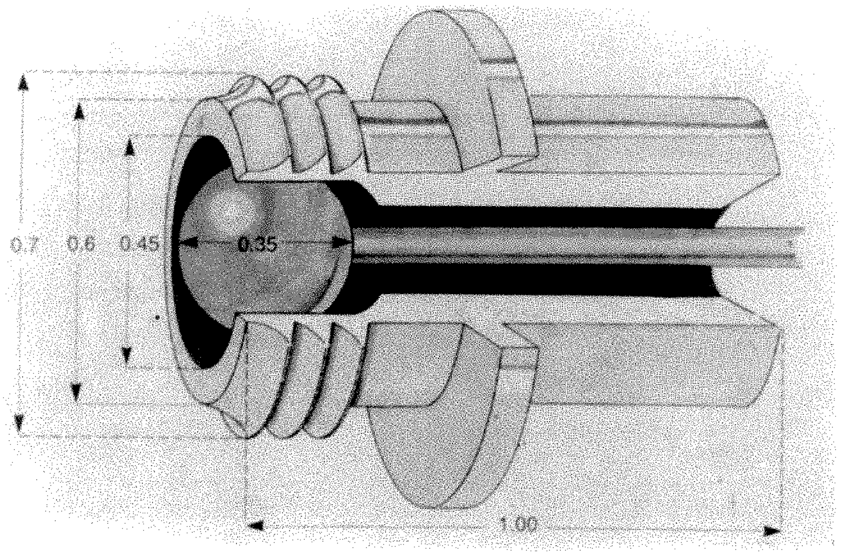

Fig 1. Schematic drawing of lateral wall implant demonstrating dimensions (in millimeters) of titanium housing surrounding platinum-iridium connecting lead and ball electrode.

The present studies were designed to further characterize the stability and tolerance of titanium implantation of the cochlear wall, and to further evaluate the responses to electrical stimulation from sites in the cochlear wall. We investigated the performance of redesigned titanium implants, housing platinum-iridium electrodes, placed in the lateral wall of the cochlea in congenitally deaf dalmatian dogs, behaviorally trained, unilaterally deafened monkeys, and unilaterally deaf human volunteers.

METHODS

MATERIALS

Microimplants were machined from commercially pure (99.7%) nonalloyed titanium. The titanium mount formed a housing around a platinum-iridium ball electrode and connecting lead (Fig 1). The connecting lead and ball electrode were supported and insulated within the titanium mount with Silastic rubber. The lead wire was insulated with Teflon. The implant measured 1.0 mm in total length with a length of 0.5 mm distal to the central flange. Smaller flanges on the distal aspect of the implant were designed to increase the surface area of the implant shaft that was in contact with otic capsular bone.

Scala tympani electrodes, placed in addition to the cochlear wall implants, in canine subjects consisted of a 4-ring electrode array adaptation of the Nucleus cochlear implant (Nucleus Ltd, Lane Cove, Australia).

SUBJECTS

Animals. All animals were cared for and sedated or anesthetized for procedures where appropriate in accordance with the guidelines of the National Institutes of Health. We placed 12 cochlear wall microimplants in the animals. One implant was placed in each of the left ears of 6 congenitally deaf dalmatian dogs at 5 to 6 months of age. Deafness was confirmed by auditory brain stem response (ABR) testing. Each ear was also implanted with a 4-channel scala tympani electrode through a cochleostomy drilled adjacent to the round window. One to 3 implants were placed in the right ears of 3 adult macaque monkeys.

Clinical Subjects. Patient 1 was a 74-year-old man with intractable vertigo associated with Meniere's disease of the right ear. He had been without useful hearing (speech reception threshold over 90 dB) on the right side for 5 years. A single cochlear wall implant was placed in the lateral wall of the cochlear apex following labyrinthectomy and was activated intraoperatively.

Patient 2 was a 38-year-old woman with chronic suppurative otitis media who had been without useful hearing in the right ear for 6 years. In conjunction with revision mastoidectomy for active infection, a single cochlear wall electrode was placed in the apex of the cochlear wall and activated postoperatively.

Patient 3 was a 43-year-old man with chronic suppurative otitis media who had been without useful hearing in the left ear for 30 years. Preoperative otoscopy demonstrated recurrent cholesteatoma within his mastoid cavity. In addition, a computed tomography scan of the temporal bones demonstrated left cochlear ossification. In conjunction with a revision mastoidectomy, the patient was implanted with 2 cochlear wall electrodes: 1 adjacent to the basal turn and 1 at an apical location. Of note, no perilymph fluid was obtained with fenestration of the cochlear wall.

Patient 4 was a 51-year-old man with intractable vertigo associated with Meniere's disease of the right

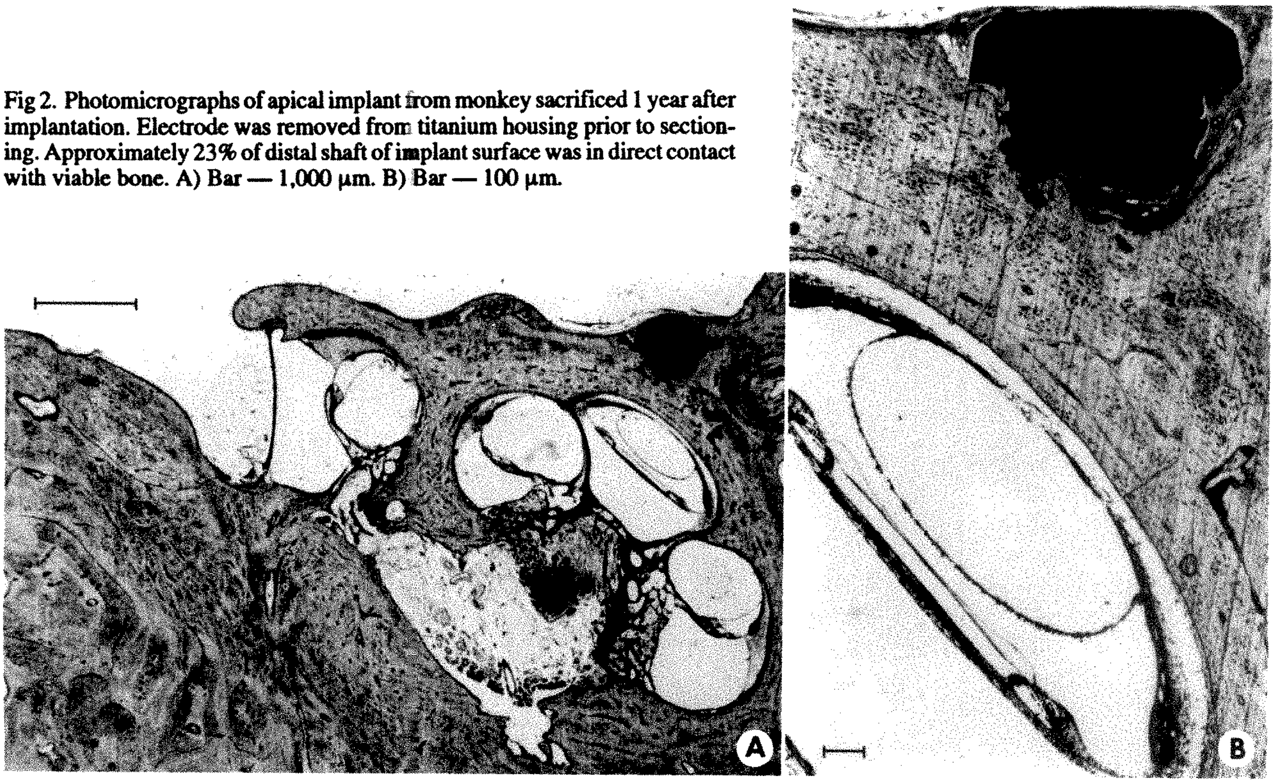

Fig 2. Photomicrographs of apical implant from monkey sacrificed 1 year after implantation. Electrode was removed from titanium housing prior to sectioning. Approximately 23% of distal shaft of implant surface was in direct contact with viable bone. A) Bar — 1,000 μm. B) Bar — 100 μm.

ear. He had been without useful hearing in the right ear for approximately 10 years. A single cochlear wall implant was placed in the lateral wall of the cochlear apex following labyrinthectomy.

SURGICAL PROCEDURES

Animal Implantation. The cochlea was exposed in the monkeys and dogs through a canal-wall-down transmastoid approach. The lateral cochlear wall was drilled to accept the implants with a microdrill (0.6-mm bur) at sites on the promontory corresponding to the basal turn and middle turn and anteroinferior to the cochleariform process (adjacent to the semicanal) at a site corresponding to the apical turn.[9] The power source for the microdrill was fitted with a rheostat that permitted reduction of the drill speed to approximately 100 rpm for cochlear wall drilling. The track was drilled to a level at which the cochlear wall changed character[9] or was no longer palpable, or until a fluid (perilymph) return was noted. Microimplants were then fit into the drill tracks.

Human Implantation. The cochlea with exposed through a facial recess (patients 1 and 4) or a canal-wall-down mastoidectomy (patients 2 and 3) approach. The cochlear wall was drilled approximately 2 mm anteroinferior to the cochleariform process.[9] In patient 3 a second implant was placed 3 mm anterior to the round window niche. Implants were removed either intraoperatively (patient 1) or 48 hours postoperatively (patients 2 through 4).

HISTOLOGIC PROCEDURES

Dogs were painlessly sacrificed 4 months following implantation in accordance with a protocol designed to evaluate the effects of prosthetic stimulation on nerve survival. Monkeys used for histologic analysis were painlessly sacrificed 12 months following implantation.

For sacrifice, the animals were anesthetized with sodium pentobarbital. Systemic and perilymphatic perfusion with Karnovsky's solution was performed. Temporal bones were harvested and trimmed. Implants with surrounding bone were embedded in acrylic resin under vacuum, cut with an Exact cutting grinding system to a thickness of 150 μm, and stained and ground to a thickness of 10 μm with toluidine blue light microscopic histomorphometry.[10] Bone-to-metal contact was calculated with a Leitz Microvid Analyzer coupled with an IBM XT computer.

FUNCTIONAL MEASURES

Animal Studies. Cochlear wall and scala tympani electrodes implanted in dogs were chronically stimulated beginning 1 month after implantation. The threshold current for obtaining a middle latency response (EMLR) was determined at the time of electrode activation. The EMLRs were recorded from an active (contralateral temporal cortex) electrode referenced to a midline scalp electrode. A noncephalic

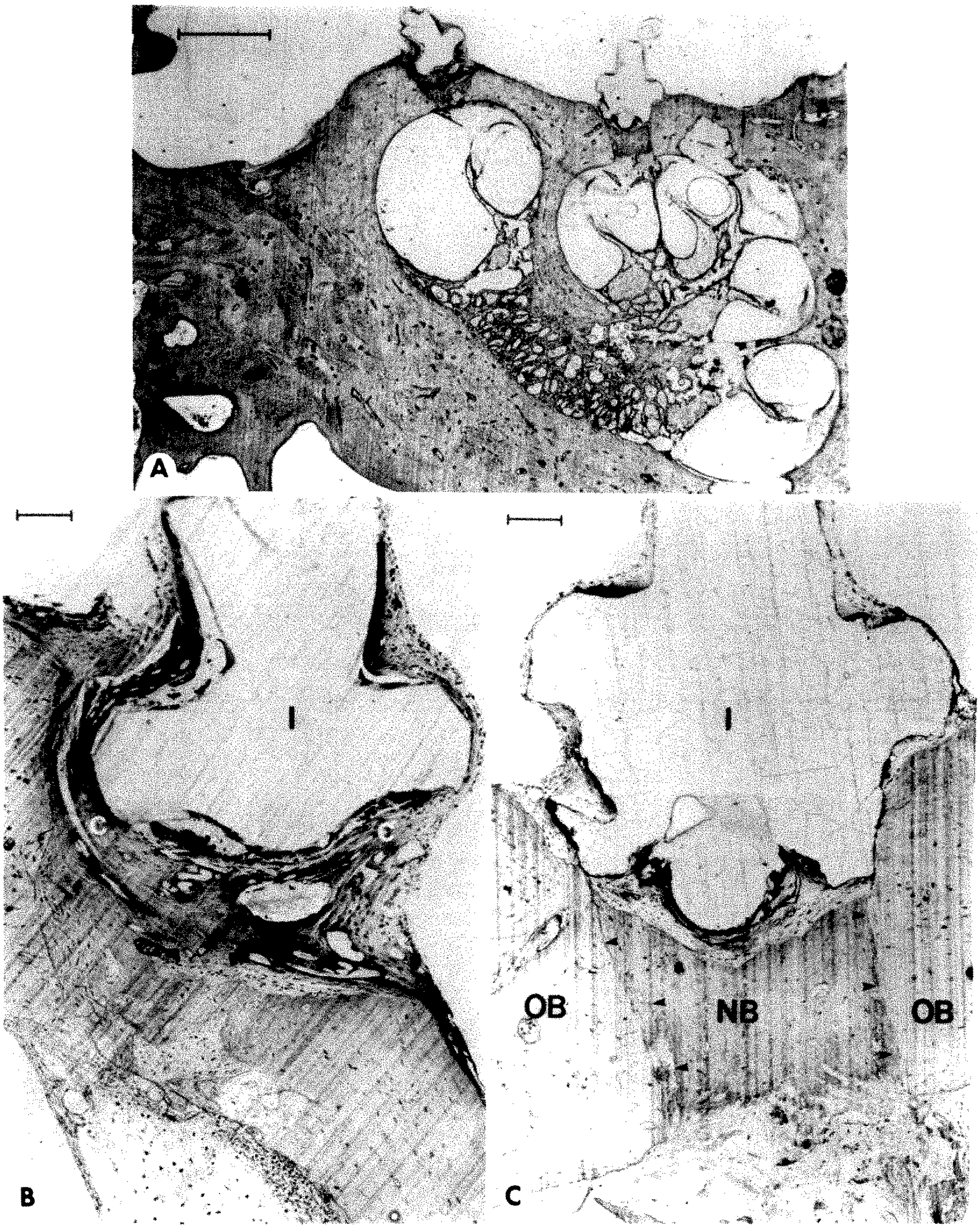

Fig 3. Implants in monkey cochlea. A) Basal and middle turn implants. Bar — 1,000 μm. B) Basal implant (I) was encapsulated with fibrous tissue capsule (C) and only loosely fixed at autopsy. Bar — 100 μm. C) Middle turn implant (I) demonstrated 8% direct osseous contact with its distal shaft. New bone (NB) developed within drill track of cochlear wall. OB — old bone, arrowheads — border of old bone and new bone, bar — 100 μm.

subcutaneous electrode served as the ground. Biphasic (leading pulse positive), charge-balanced pulses at 2.5 milliseconds per phase were delivered at a frequency of 10/s by a current generator worn by the dog in a jacket. The EMLR thresholds were determined with various combinations of stimulating electrodes. Stimulating electrode configurations that were evaluated included 1) intrascalar bipolar stimulation and 2) intrascalar electrode to cochlear wall electrode. A cochlear wall–to–surface electrode stimulating montage failed to produce reliable EMLR waveforms.

One of the monkeys was tested for its ability to discriminate stimulation of one cochlear wall electrode, located near the cochlear apex, from another, located in the promontory. The monkey had previously been trained on frequency and level discrimination tasks and then was tested on an electrode place

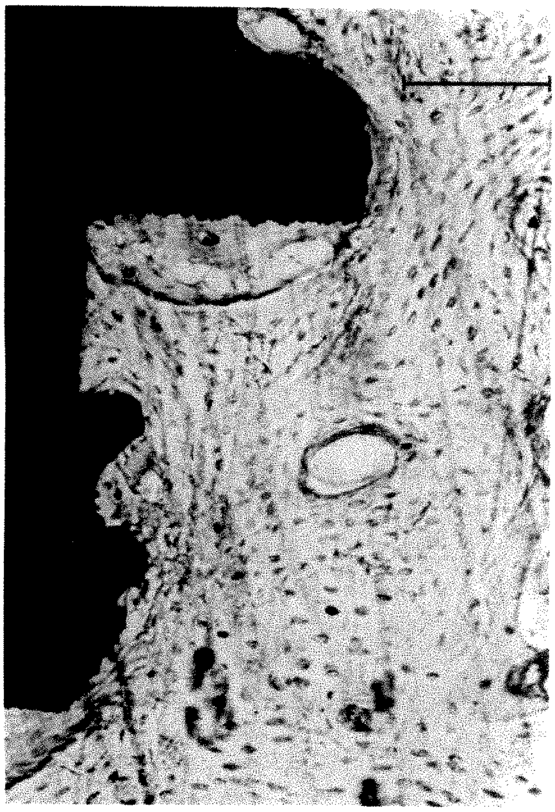

Fig 4. Titanium cochlear wall implant from dog implanted 4 months prior to death. Approximately 16% of distal shaft of implant was in direct contact with viable bone. Bar — 100 μm.

discrimination task.[11] In the electrode place discrimination task the monkey received a repeating stimulus to 1 electrode during a foreperiod of randomly variable duration, followed by repeating stimulus to the other electrode during a 1-second observation period that was otherwise unmarked. The stimuli were delivered in trains of 200 milliseconds on and 100 milliseconds off. The place of stimulation was changed during one of the stimulus-off periods, with no change in the timing of stimulus delivery. Responses to the stimulus change within 1 second were reinforced and were counted as correct detections. Catch trials (trials on which the stimulation site did not change) were also run. Both electrodes were stimulated in a monopolar configuration with the return electrode located on the surface of the skull. In separate tests electrical white-noise stimuli and 100-Hz sinusoids were used to stimulate the electrodes. The animal was tested at levels equivalent to 20%, 50%, and 80% of the dynamic range as estimated by reaction time.[12] In an attempt to counter any changes in loudness that might be associated with the change in the stimulation site, the level of the stimulus to the test electrode was varied in 0.25-dB steps around the estimated equal loudness point.[13]

THRESHOLDS IN CANINES

	Middle Latency Response Threshold		*Facial Nerve Stimulation Threshold*
Dog	*Bipolar Intrascalar Electrodes*	*Monopolar Cochlear Wall Referenced to Intrascalar Electrode*	*Monopolar Cochlear Wall Referenced to Intrascalar Electrode*
1	100-150	200	300
2	150	150	>800
3	200	250	>800

Data are currents in microamperes peak to peak.

Clinical Studies. Patient 1 was stimulated preoperatively and again postoperatively (following implantation and removal of the cochlear wall implant) by transtympanic promontory stimulation. Biphasic rectangular charge-balanced square waves at 50, 100, 200, and 400 Hz were delivered in a 50% duty cycle mode (500 milliseconds on and 500 milliseconds off) by a Teflon-insulated tungsten needle electrode placed on the promontory transtympanically following local anesthesia. A surface electrode attached to the ipsilateral earlobe served as the return electrode.

Following the placement of the cochlear wall electrode in patient 1, pulsatile stimulation was delivered by means of a return electrode placed anterior to the tragus of the stimulated ear. Responses were recorded with subdermal needle electrodes placed at the vertex and the contralateral earlobe. The EMLRs were evoked by means of biphasic current pulses with a duration of 2.5 milliseconds per phase presented at the rate of 10/s. Electrical auditory brain stem responses (EABRs) were elicited by biphasic pulses (200 microseconds per phase) at the rate of 10/s. The EMLRs were recorded with a filter band pass of 10 to 500 Hz, and the EABRs were recorded with a band pass of 10 to 1,000 Hz. Thresholds were established by means of visual inspection of the recorded waveforms. In order to avoid undue interference with the EMLR by anesthetic agents, a balanced narcotic–nitrous oxide anesthesia was used.

Stimulation of cochlear wall electrodes was carried out in patients 2, 3, and 4, 24 hours postoperatively. The stimuli and the stimulation paradigm were identical to those described for preoperative transtympanic promontory stimulation. The only difference was that the electrical current was delivered to the cochlear wall electrode, with an external reference electrode serving as the return.

RESULTS

ANIMAL STUDIES

Histology. Figures 2 and 3 demonstrate histologic cross sections at the approximate centers of titanium

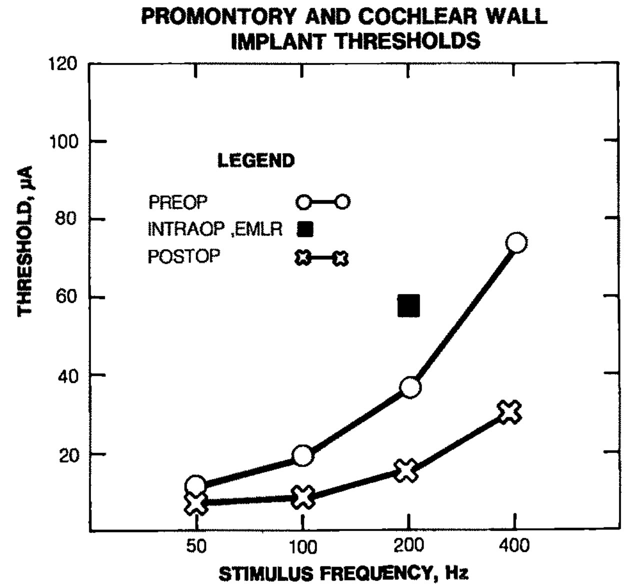

Fig 5. (Patient 1) Perioperative behavioral thresholds for promontory stimulation and intraoperative middle latency response (EMLR) thresholds for stimulation of cochlear wall electrode. All thresholds are in microamperes peak to peak.

implants placed in a monkey lateral cochlear wall. At autopsy there was evidence of granulation tissue in the middle ear of this monkey. The apical and middle turn implants were rigidly fixed, whereas the basal implant was loosely attached to the promontory. Figure 2 shows an apically placed implant for which approximately 23% of the surface of the distal shaft was in direct contact with bone. This electrode did not penetrate the scala, and the adjacent endosteum is intact. Figure 3 demonstrates implants placed in sites corresponding to the middle and basal turns of the cochlea. Figure 3C is a high-power view of the middle turn implant demonstrating disruption of the underlying endosteum and new bone formation within the deeper portion of the cochlear fenestration. More laterally within the fenestration, a fibrous "ghost" of the implant indicates that approximately 8% of the implant shaft was in direct contact with bone. Figure 3B shows a fibrous capsule of the loosely fixed basal turn implant. No direct bony contact with the implant was demonstrated. Although drilling did not disrupt the underlying endosteum, new bone formation limited to the deeper portion of the track is apparent.

Figure 4 demonstrates a high-power photomicrograph of an apically placed canine implant. Approximately 16% of the implant shaft was in direct contact with viable bone.

Overall, 11 of 12 implants (91.6%) placed in dogs and monkeys were rigidly fixed at the time of autopsy. Six of the rigidly fixed implants were examined histologically and demonstrated bone-to-metal contact over 8% to 23% of the distal implant shaft. In regions not directly in contact with bone, the implant shaft was surrounded with fibrous tissue devoid of inflammatory cells. In addition, some areas not directly in contact with bone demonstrated osteoid tissue that may not have been properly calcified at the time of sacrifice. Inspection of the sensory and neural elements adjacent to the drilled areas revealed limited, if any, damage to these structures.

Electrophysiology. Three of 6 dogs maintained intact connecting leads and percutaneous connectors throughout the 4-month period following implantation. The EMLR threshold data were obtained twice monthly for these dogs, and they remained stable over the 4-month period. Thresholds were slightly lower for intrascalar electrodes than for cochlear wall implants in 2 of the dogs (see Table). The EMLR thresholds for intrascalar and cochlear wall stimulation sites were below those associated with adventitial facial nerve stimulation.

Electrode Place Discrimination. The ability of 1 of the monkeys to discriminate stimulation of an electrode site at the apex from one in the promontory was tested by means of an electrode place discrimination paradigm (described in Methods). Ninety-seven percent to 100% discrimination was achieved at all levels with minimal practice. Small changes in the level of the test stimulus relative to the reference stimulus level did not result in reduced discrimination at any of the levels tested. This finding suggests that the discrimination was not based on loudness cues (or at least those that could be countered by an adjustment in stimulus intensity).

CLINICAL TESTING

The EMLR threshold obtained intraoperatively in patient 1 for pulses of 2.5 milliseconds per phase at 10/s was 58 µA peak to peak (Fig 5). This value is within the +1 SD range of successful cochlear implant patients stimulated preoperatively with a transtympanic needle.[14] The EABR threshold for pulses of 200 milliseconds per phase at 10/s was 400 µA peak to peak, which was also within the range associated with preoperative transtympanic stimulation in our cochlear implant users.

Preoperative and postoperative behavioral thresholds for promontory stimulation in patient 1 showed lower thresholds following implantation and removal of the cochlear wall implant (Fig 5).

Postoperative stimulation of the cochlear wall implant in patient 2 demonstrated behavioral responses to 3 of 4 frequencies investigated (Fig 6). Thresholds for the low-frequency square waves (50 and 100 Hz) were comparable to thresholds obtained with transtympanic stimulation in our cochlear im-

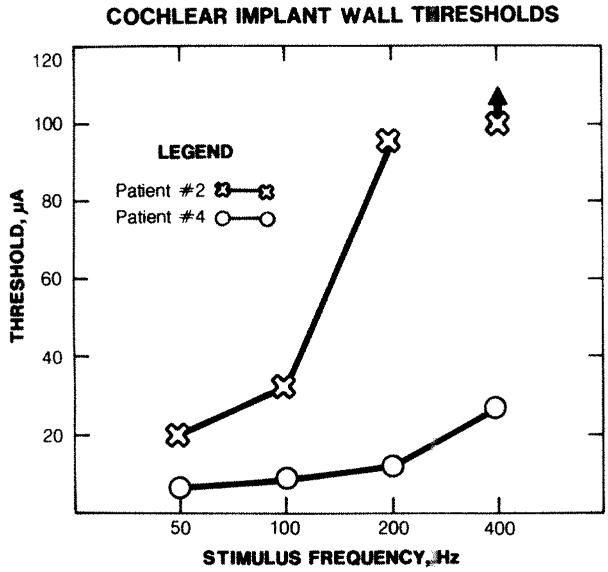

Fig 6. (Patients 2 and 4) Threshold versus frequency functions for postoperative behavioral responses to stimulation of cochlear wall electrodes. Thresholds are in microamperes peak to peak.

plant patient group. For higher (200 and 400 Hz) stimulus frequencies, thresholds exceeded the +2 SD range.

Attempts to obtain auditory sensations with the stimulation of these implanted electrodes failed in patient 3. No responses were obtained for any of the stimuli at the output limits of the stimulator used in the clinical trial (500 μA peak to peak).

Postoperative stimulation of the cochlear wall implant in patient 4 produced behavioral responses at the 4 frequencies tested (Fig 6). All threshold measurements in this patient were within the range of current intensities associated with preoperative transtympanic stimulation in patients who became successful cochlear implant users in our cochlear implant program.[14]

DISCUSSION

ANIMAL HISTOLOGY

The histologic results of our animal implantations demonstrate that titanium fixtures are capable of forming a stable anchorage in the lateral cochlear wall. Subtotal bone contact with the implant appears to confer this stability. While a variety of factors are probably involved in producing complete integration of titanium with bone, several factors in particular stand out. The implant material must be biocompatible and should have surface grooves to facilitate cellular and bone attachment.[7] Implant sites should be prepared with a careful drilling technique that produces a threaded implant site and that does not elevate the temperature of surrounding bone beyond 47°C.[15] By avoiding excessive heating of the surrounding bone, cellular viability is maximized. A threaded implant site maximizes the implant-to-bone area of contact and produces early resistance to shearing.

The implants evaluated in this report were placed without the benefit of a high-torque, low-speed drill (less than 20 rpm),[7] required for atraumatic preparation of implant sites. Moreover, these implants were placed in unthreaded sites.

Although the nonosseous tissue surrounding the implants showed little adverse histologic reaction, new bone growth within cochlear drill tracks was apparent in one monkey, in which otitis media was present at autopsy. This new bone growth occurred in 2 drilled sites: 1 with, and 1 without disruption of the endosteum lining the underlying scala. It remains to be determined whether this new bone growth could be prevented by an implant completely occupying a cochlear fenestration. It should also be noted that areas surrounding the implants that were not directly in contact with bone in some cases demonstrated uncalcified osteoid tissue. It is unknown whether this tissue might have undergone calcification given a longer duration of implantation.

FUNCTIONAL MEASURES

Animal Studies. Our animal trials using congenitally deaf dalmatians demonstrated stable electrophysiologic thresholds over a 4-month period. Thresholds for scala tympani implants were slightly lower than those of the cochlear wall implants. This finding is predictable, since the cochlear wall implant is physically more distant from the target neural elements. Variation in thresholds between animals may be explained by differences in electrode position and/or differences in auditory nerve survival.

Electrophysiologic trials in dogs also demonstrated that the threshold for eliciting an EMLR was below that required for producing adventitial facial nerve stimulation. This suggests that placing a stimulating electrode that is housed in titanium within the cochlear wall effectively directs current to the auditory nerve and not, at least not effectively, to the fallopian canal. This does not, however, exclude the possibility that the current path pursued an indirect course through the round window.

The ability of the nonhuman primate to discriminate stimulation of one electrode site from that of another suggests that different populations of nerve fibers are being stimulated by electrodes located some distance apart in the cochlear wall, even when monopolar stimulation is used. It remains to be determined how closely the electrodes can be spaced without impairing their discriminability.

Human Studies. Our preliminary experience with clinical application of titanium cochlear wall implants demonstrated electrophysiologic or perceptual response in 3 patients with patent cochleas. In these patients, stimulation with cochlear wall electrodes produced auditory responses at thresholds below those for facial or tympanic nerve stimulation. In 1 of these patients (patient 1), investigated intraoperatively with evoked potentials, electrophysiologic thresholds were within the range established by transtympanic stimulation of cochlear implant candidates who later became successful cochlear implant users. Furthermore, a comparison of preoperative and postoperative promontory stimulation results in this patient indicated that the acute placement and subsequent removal of the cochlear wall implant did not impair auditory responsiveness to electrical stimulation. Postoperative thresholds for transtympanic stimulation were lower than those obtained before labyrinthectomy. The presence of the postoperative cochleotomy may have contributed to the reduced threshold.

Our single patient with long-standing deafness and cochlear obliteration did not perceive auditory sensation with cochlear wall stimulation. This probably reflects a lack of viable innervation of the implanted cochlea.

The absence of facial nerve stimulation and lack of pain sensation with activation suggest that an implant site within the cochlear wall and encasement of the electrode with a titanium housing adequately directs current to minimize adventitial stimulation in the human cochlea as well.

CONCLUSIONS

The results of these studies extend prior observations that nonalloyed titanium implants are capable of developing direct contact with otic capsular bone. Although the bony contact was not complete, it appears to confer stability to cochlear wall electrodes. New bone growth may occur within cochlear wall drill tracks, perhaps in response to inflammation, with and without endosteal disruption.

Combined data from animal clinical trials suggest that cochlear wall electrodes are capable of producing auditory percepts at thresholds below those for tympanic and facial nerve stimulation. Place specificity of stimulation may be achieved with this strategy of cochlear wall implantation. Thresholds in successfully stimulated patients are comparable to those of transtympanic promontory stimulation of patients who subsequently were implanted with and successfully used scala tympani implants.

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Ann Otol Rhinol Laryngol 102:1993

THE HAYEK OSCILLATOR: A NEW METHOD OF VENTILATION IN MICROLARYNGEAL SURGERY

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The Hayek oscillator is an externally (body) mounted cuirass ventilator used in the intensive care unit. We have used it to ventilate patients undergoing microlaryngeal surgery. It was found to be a relatively safe method of ventilation in these cases, with the advantage of dispensing with any form of endolaryngeal or endotracheal intubation.

KEY WORDS — anesthesia, larynx, surgery.

MATERIAL AND METHODS

The Hayek Oscillator (Flexco Instruments AG, Zurich, Switzerland) consists of a chest enclosure (cuirass), a power unit, and a control unit. The cuirass is made of clear, flexible lightweight plastic edged with a foam skirt that fits on the anterior surface of the lower chest and upper abdomen, held in close approximation to the patient's body by being clamped to a plate placed underneath the body. The cuirass is connected to the power unit with wide bore tubing (Fig 1). Within the power unit is a diaphragmatic pump with a maximum stroke of 3.5 L. This pump can operate over a wide range of frequencies, 8 to 999 cycles per minute (CPM). The pump generates an oscillating pressure around this frequency. A further pump enables this oscillation to be superimposed on a negative baseline, permitting the control of lung volume (Fig 2). The frequency, inspiratory pressure, expiratory pressure, and inspiratory-expiratory ratio can be set on the automatic control unit, which then

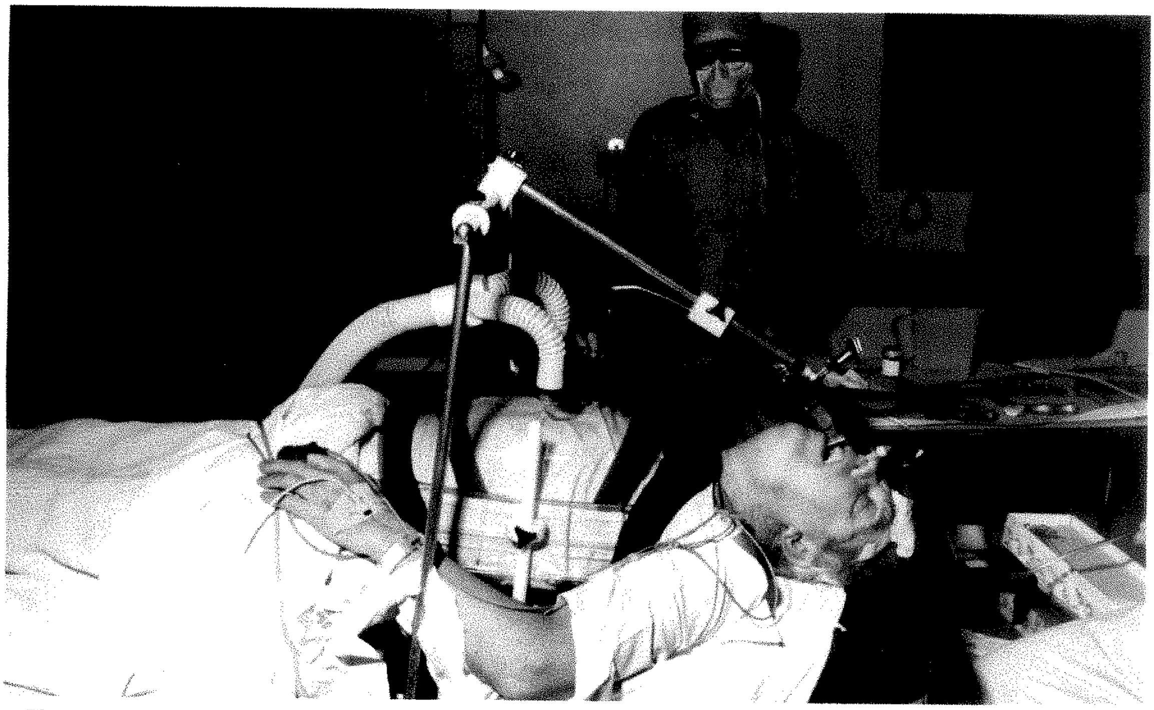

Fig 1. Foam rubber-skirted cuirass is attached by lightweight transparent plastic rods to plate underneath patient. Cuirass is connected to oscillator pump via wide-bore tubing, which is ventilating patient. Kleinsasser endoscope is in place, supported by adapted suspensory apparatus.

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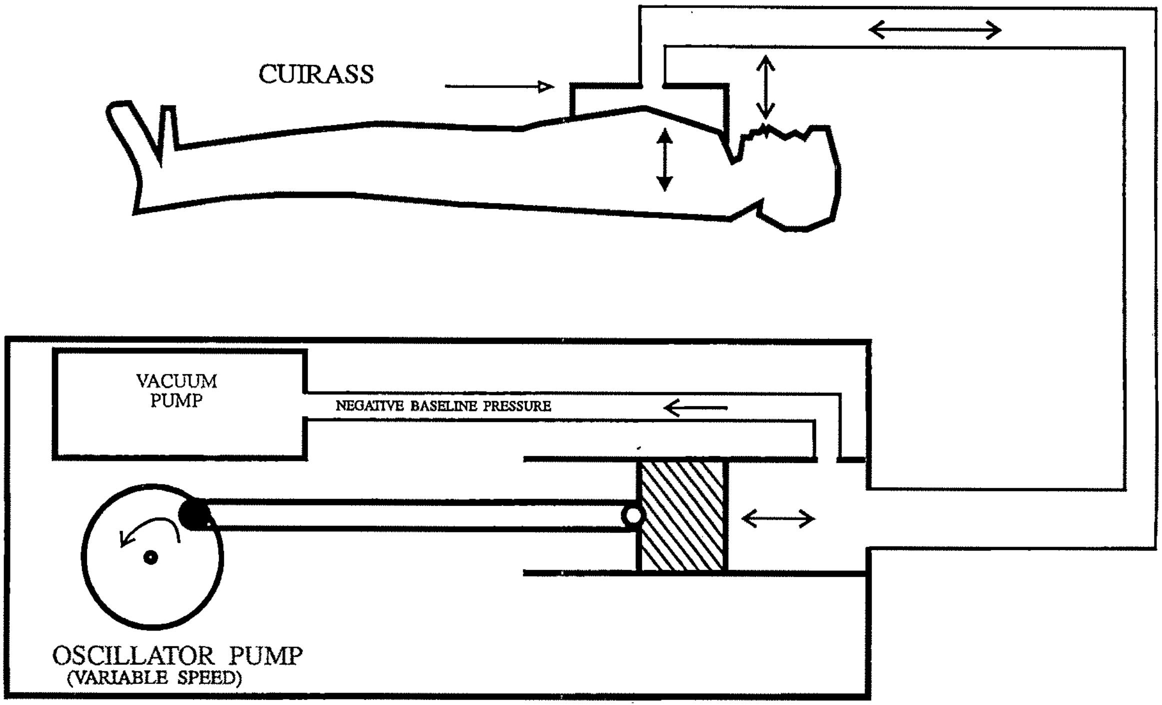

Fig 2. Schematic diagram of principles behind Hayek oscillator. Two-headed arrows demonstrate oscillating flow of air.

adjusts the performance of the power unit by negative feedback from a pressure transducer connected to the inside of the cuirass.[1-6]

Since both the inspiratory and expiratory phases are controlled, high frequencies can be achieved. This is in contrast to negative pressure ventilation, which depends during the expiratory phase on passive recoil of the chest, limiting sharply the attainable frequencies.

Twenty-five patients (9 women and 16 men) 25 to 75 years of age, all of whom required upper airway endoscopy, were allocated to the study. Informed consent was obtained from all patients, and ethical committee approval was obtained. The weight range of the patients was 52 to 105 kg (median 69.8 kg). Details of surgical procedures are summarized in the Table; procedure duration ranged from 5 to 30 minutes (median 16 minutes).

Anesthesia was induced with intravenous propofol and maintained with a propofol infusion administered by means of a syringe pump. Muscle relaxation was obtained with intravenous bolus doses of suxamethonium chloride. Following the induction of anesthesia, a nasopharyngeal airway was inserted. This assisted the maintenance of a clear airway until the cuirass was fitted and was used to enrich the oxygen content of the inspired air. Hemoglobin oxygen saturation was monitored with a transcutaneous pulse oximeter. The end-tidal carbon dioxide (CO2) was measured before the cuirass was attached, and at the end of the operation. A microcamera was attached to the side arm of the microscope to enable the anesthetist to accurately assess cord paralysis and bleeding, and allow indirect surgery if required.

RESULTS

To obtain adequate ventilation with minimal or no vocal cord movement, we examined the following settings: frequency range 30 to 300 CPM, cuirass inspiratory pressures of −15 to −30 cm H2O, cuirass expiratory pressures of +5 to +12 cm H2O, and inspiratory-expiratory ratio 1:1 to 1:3.

It was found that by increasing the frequency, the cuirass ventilating pressures could be reduced, thus reducing the vocal cord movement. At frequencies above 120 CPM, however, general body movement became a factor, increasing the movement of the operative field. The optimum situation therefore occurred at 120 CPM, an inspiratory-expiratory ratio of 1:1, an expiratory pressure +5 to +7 cm H2O, and an inspiratory pressure of −15 to −20 cm H2O, producing a net airway pressure of +4 to −4 cm H2O.

Full, unobstructed surgery was possible in all cases (see Table). There were no major complications. There was one minor case of epistaxis, thought to be due to the placement of the nasopharyngeal tube. Aspiration of gastric contents did not occur, even in one patient with malignant ascites.

DIAGNOSIS AND SURGICAL PROCEDURE IN 25 PATIENTS STUDIED

Patient	*Diagnosis*	*Surgical Procedure*
1	Vocal cord polyp	Microsurgical excision
2	Singer's nodules	Microsurgical excision
3	? Vocal cord malignancy	Biopsy, staging, panendoscopy
4	? Vocal cord lesion	Microscopic examination
5	? Vocal cord lesion	Microscopic examination
6	Reinke's edema	Microsurgical excision redundant mucosa
7	Singer's nodules	Microsurgical excision
8	Singer's nodules	Microsurgical excision
9	Reinke's edema	Microsurgical excision redundant mucosa
10	? Vocal cord lesion	Microscopic examination
11	? Subglottic malignancy	Microscopic examination, biopsy
12	? Hyperkeratosis	Microsurgical excision
13	Singer's nodules	Microsurgical excision
14	? Supraglottic lesion	Microscopic examination
15	Vocal cord palsy	Panendoscopy, assess cricoarytenoid joints
16	? Vocal cord malignancy	Biopsy, staging, panendoscopy
17	Singer's nodules	Microsurgical excision
18	? Vocal cord malignancy	Biopsy, staging, panendoscopy
19	? Vocal cord lesion	Microscopic examination
20	? Vocal cord malignancy	Biopsy, staging, panendoscopy
21	Supraglottic lesion	Biopsy, staging, panendoscopy
22	? Vocal cord hemangioma	Microscopic examination
23	Singer's nodules	Ultrapulse CO2 laser vaporization
24	Vocal cord polyp	Microscopic excision
25	? Reinke's edema	Excision biopsy of hyperkeratosis

We were unable to measure end-tidal CO2 during cuirass ventilation, because the airway is completely open, with gaseous exchange occurring continually by virtue of turbulent airflow, not in a defined inspiration-expiration pattern as with other methods of ventilation. We did, however, measure the end-tidal CO2 before and immediately after the cuirass ventilation, and there was sometimes a small rise of around 10%, although in no case were these rises regarded as significant. There were also no problems with arrhythmias or other sequelae of CO2 retention. It was not thought to be ethically correct to measure arterial CO2 levels during the operation, particularly as in our operating room it takes at least 5 minutes to have the sample processed, rendering the result almost insignificant, given the duration of the procedures. In previous studies using this machine, CO2 retention was not a problem.[4]

The pulse oximetry showed no fall in arterial hemoglobin saturation from before the start of the operation to the end of the procedure, measured continuously, in all cases.

DISCUSSION

Our study has shown that the Hayek oscillator appeared to provide adequate ventilation in anesthetized, paralyzed patients without endotracheal intubation, allowing us to perform unobstructed, unhurried microlaryngeal surgery in all cases.

Other methods of ventilation, such as high-frequency jet ventilation, can provide an unobstructed visual field, but are associated with complications such as pneumothorax, air embolism, distal seeding of tumor, gastric distention, and aspiration of gastric contents.[7,8] Because of the low airway pressures involved, the Hayek oscillator appears to have none of these problems, although aspiration of gastric contents due to lack of airway protection remains a possible problem, as in most techniques in which a cuffed endotracheal tube is not used.

The absence of a tracheal tube of any sort means that airway fires are not a problem in laser surgery.[9] We found this new technique to be invaluable in the management of patients requiring microlaryngeal surgery.

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SIXTH INTERNATIONAL CONGRESS ON INTERVENTIONAL ULTRASOUND

The Sixth International Congress on Interventional Ultrasound will be held September 7-10, 1993, in Copenhagen, Denmark. For information, contact Christian Nolsøe, Congress Secretary, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

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FIRST CONGRESS OF EUROPEAN SKULL BASE SOCIETY

The European Skull Base Society will hold its first congress September 26-30, 1993, in Riva del Garda (Trento), Italy. For further information contact Carmelo Zappone, MD, Congress Secretary, Division of ORL, Ospedali Riuniti, Largo Barozzi 1, 24100 Bergamo, Italy; telephone 35-269578; fax 35-269460.

Ann Otol Rhinol Laryngol 102:1993

REGENERATION OF MAXILLARY SINUS MUCOSA FOLLOWING SURGICAL REMOVAL

EXPERIMENTAL STUDY IN RABBITS

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HUDDINGE, SWEDEN

A rapid regeneration of the epithelium takes place in the maxillary sinus in rabbits after experimental operative removal of the mucosa. Two weeks postoperatively the previously denuded areas have reepithelialized. The subepithelial glands, however, do not seem to regenerate. The normal sinus mucosa contains numerous serous glands in the lamina propria, but in the regenerated mucosa these glands are replaced by dense connective tissue. Atypical glands and polyp formations are sometimes encountered, but goblet cells are sparse. Furthermore, the sinus cavity on the operated side is reduced in size compared with the nonoperated side because of fibrosis and periosteal reactions including bone degradation and neogenesis. This study indicates that although the mucosa is reepithelialized within 2 weeks, the regeneration of the lamina propria is incomplete, and reactive cellular processes such as bone remodeling, fibroblast proliferation, and formation of polyps and "atypical glands" are characteristic of regenerating mucosa.

KEY WORDS — osteogenesis, regeneration, sinus mucosa.

INTRODUCTION

Certain surgical procedures carried out on the nasal chambers and paranasal sinuses include partial or total removal of the mucosal lining. In cases of chronic sinusitis, the Caldwell-Luc operation, with different modifications, has traditionally been the preferred treatment.[1,2] Although the mucociliary system is well able to recover from mechanical trauma, the clinical results after these procedures often have been unsatisfactory, and doubts about their efficacy have been raised.[3] The development of functional endoscopic sinus surgery has focused the operative procedure on removal of gross pathologic processes in the infundibular area close to the natural ostium.[4,5] Rather disparate results have been reported regarding the regeneration of nasal and sinus mucosa following surgical removal.[6-12] In earlier investigations made on various species such as sheep, dogs, humans, and rabbits, mainly biopsy material has been analyzed. It was therefore considered of interest to perform an experimental study on the whole sinus complex, including the underlying bone, after surgical removal of the sinus mucosa. In certain respects, the rabbit maxillary sinuses resemble those of humans; they have a well-defined ostium[13] and are fairly large and readily accessible.

The regrowth of the mechanically denuded sinus mucosa was investigated at various postoperative intervals from 1 week to 9 months, and the resulting data were compared with previously published results on the sequential events of the regeneration of respiratory mucosa.

MATERIAL AND METHODS

Seventeen New Zealand White rabbits of either sex and with a body weight of 3.0 to 4.2 kg were used. The experimental setup was approved by the Animal Ethics Committee at Huddinge Hospital.

The animals were anesthetized with a subcutaneous injection of diazepam (Stesolid Novum) and with an intramuscular injection of Hypnorm. Following skin incisions, the superior parts of the rabbit maxillary sinuses were exposed through a hole drilled through the dorsal wall of the sinus on both sides. The

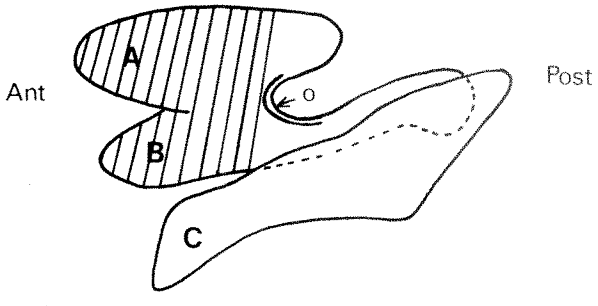

Fig 1. Schematic drawing of right sinus cavity seen from medial aspect. Upper (A), middle (B), and lower (C) compartments are seen. Crescent-shaped ostium (O) is indicated by arrow. Hatched area shows region of sinus mucosa removed in present investigation. Broken line shows inferior limit of posterior part of middle compartment. Ant — anterior, Post — posterior.

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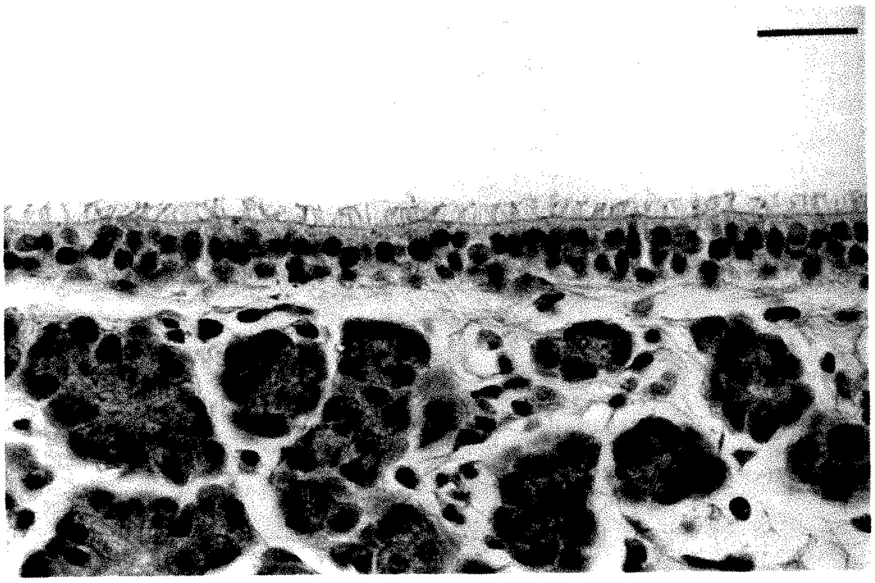

Fig 2. Rabbit normal maxillary sinus mucosa with pseudostratified ciliated epithelium situated on basal membrane. Below basal membrane is lamina propria with numerous serous glands. Bar — 30 µm.

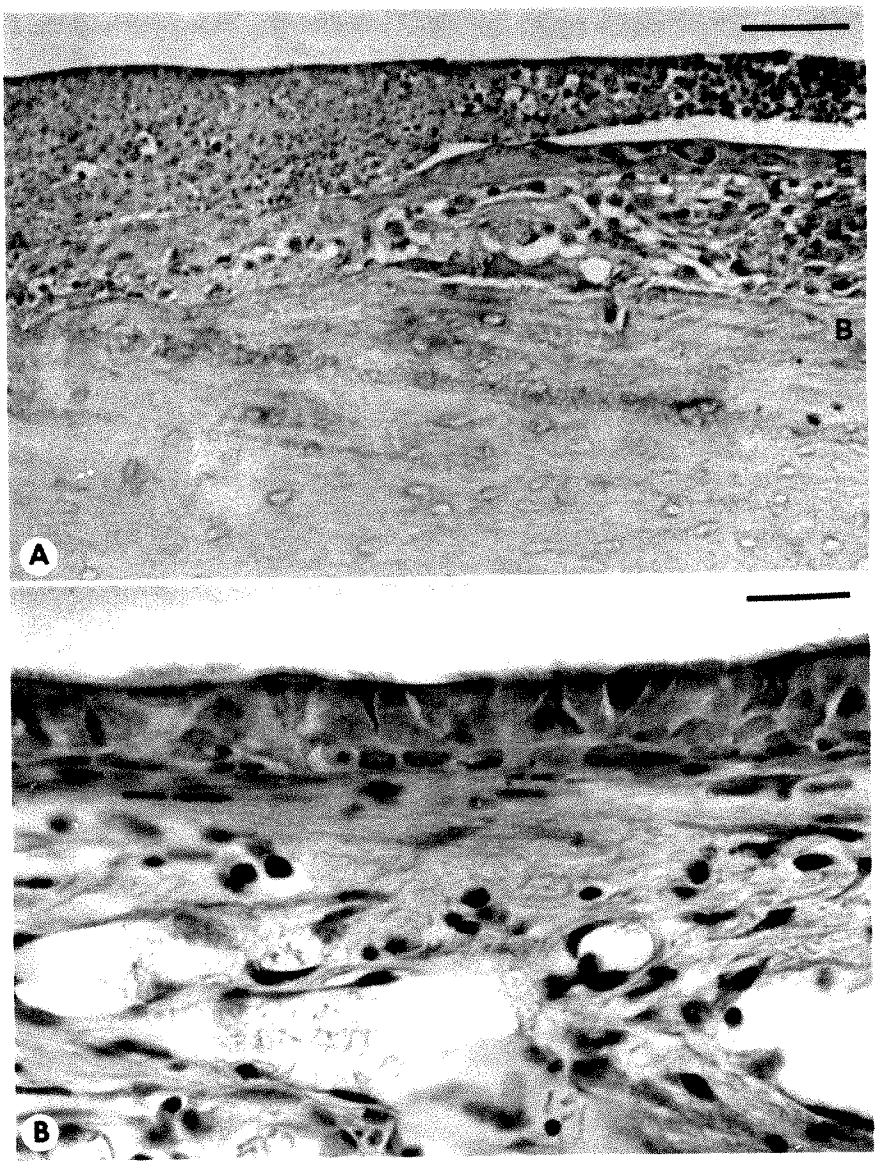

Fig 3. Rabbit maxillary sinus epithelium. A) One week postoperatively. Epithelium (E) consists mainly of poorly differentiated cells. Section shows numerous fibroblasts and collagen in lamina propria (L). Inflammatory cells are seen in secretion (S). B — bone, bar — 100 µm. B) Two weeks postoperatively. Further differentiation toward ciliated epithelium. Newly formed vessels are seen in lamina propria. Bar — 30 µm. (Continued on next page.)

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anterior part of both the upper and middle compartments of the sinuses was thus exposed, and the mucosa of the anterior part of the sinus was completely removed unilaterally without interfering with the ostium (Fig 1). The procedure was performed with an operating microscope and with middle ear microinstruments. After operation the skin incisions were closed with polyglycolic acid sutures. The animals were left to heal and then were sacrificed painlessly after various intervals: 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, and 9 months postoperatively. After decapitation and dissection the entire nose complex, including the nose and sinus cavities, was fixed in buffered 4% formaldehyde. The bony nose complex was decalcified with phosphate-buffered ethylenediaminetetraacetic acid. After dehydration and paraffin embedding, the specimens were sectioned at 5 µm. The sections were stained with hematoxylin and eosin, Alcian blue–periodic acid–Schiff, and van Gieson connective tissue stains and were studied by light microscopy.

RESULTS

The normal rabbit maxillary sinus mucosa consists of a pseudostratified (two or three layers) ciliated epithelium with ciliated cells, goblet cells, basal cells, and some intermediate cells on a basal membrane. The existence of goblet cells in the rabbit maxillary mucosa has been questioned[14]; whatever the case, ciliated cells outnumber other types of cells in the sinus. Below the basal membrane, close to the adjacent facial bones, is the lamina propria, which contains numerous serous glands and vessels (Fig 2). In contrast, the human maxillary sinus has very few glands, and most of these are located around the ostium.[15] At the time of sacrifice the animals showed

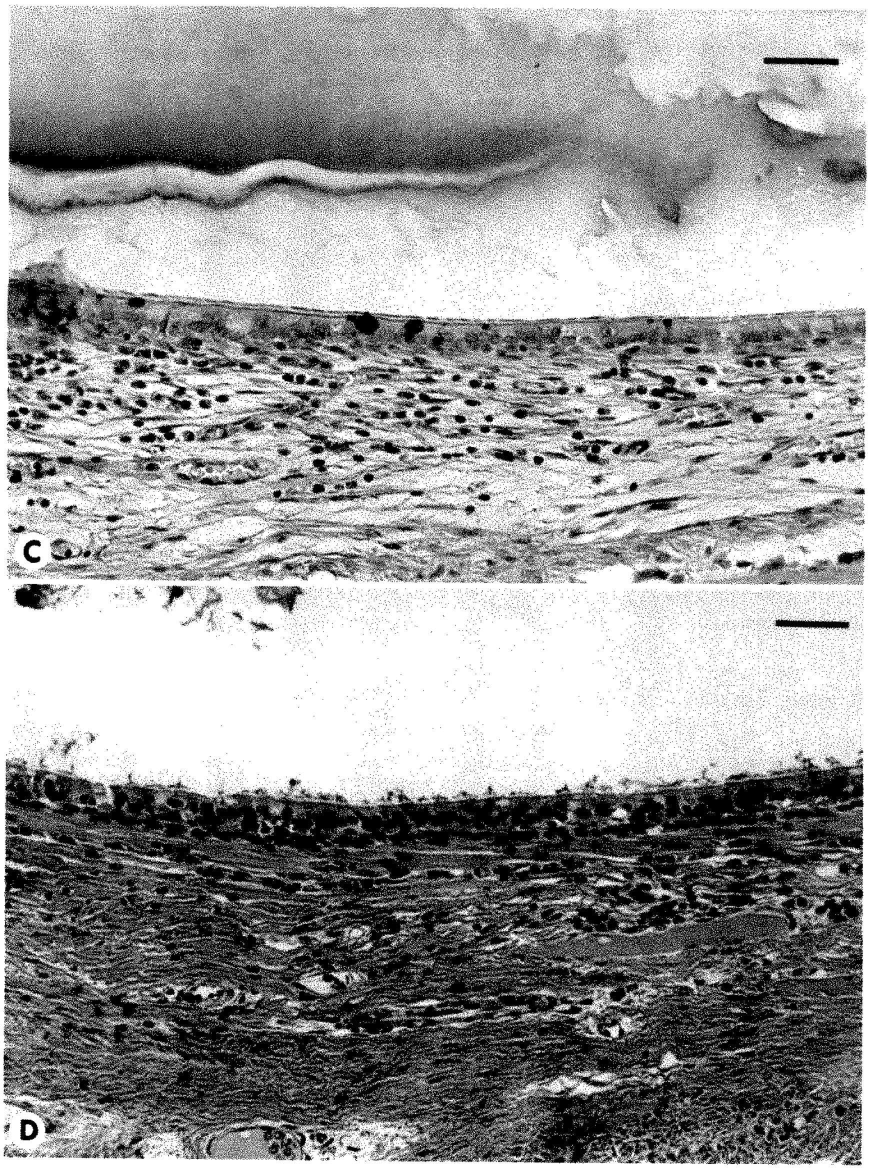

Fig 3, continued. C) Two months postoperatively. Sinus is lined by epithelium similar to that of normal mucosa, with mainly ciliated cells. In this section some goblet cells can be seen. Bar — 100 µm. D) Four months postoperatively. Normal structure of epithelium. Lamina propria is devoid of serous glands. Note dense connective tissue. Bar — 100 µm.

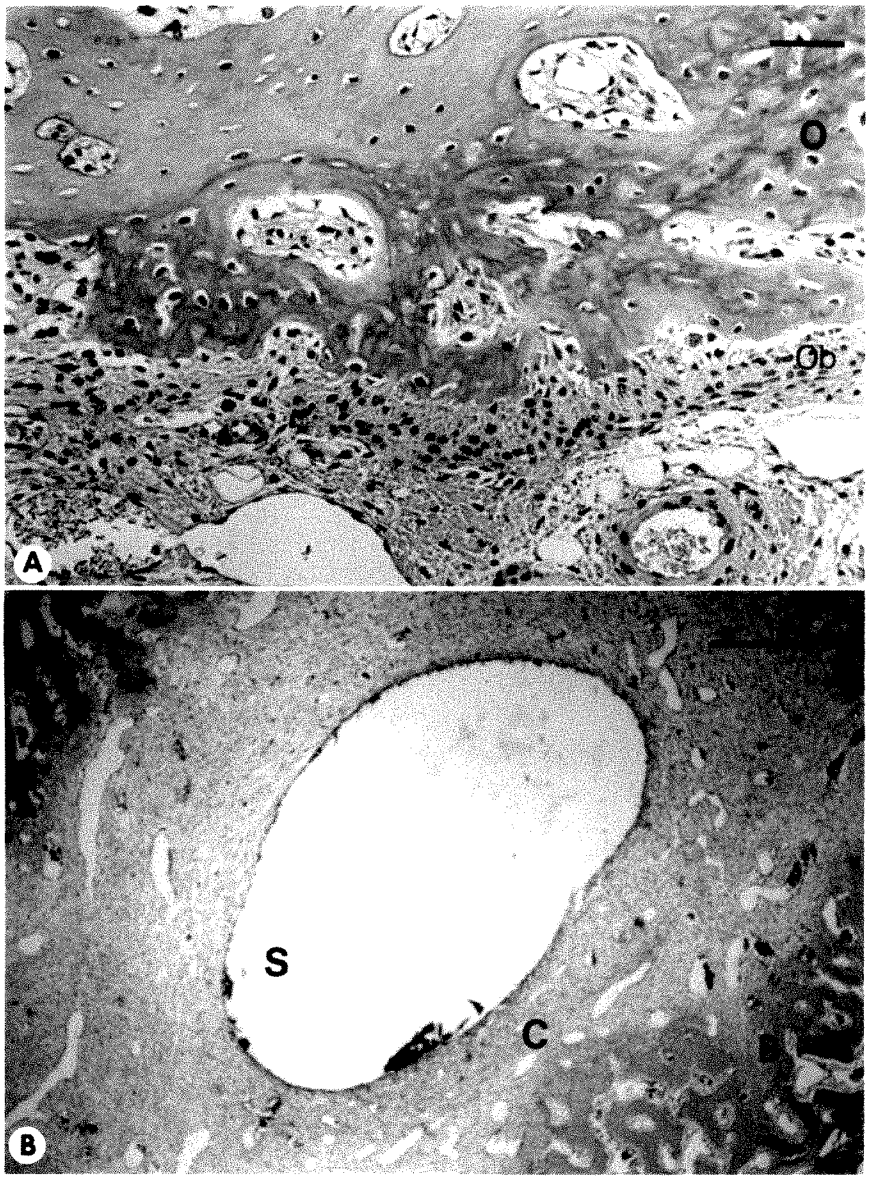

Fig 4. A) One week postoperatively. New bone formation is seen with osteoid (O) and palisades of osteoblasts (Ob). Bar — 100 µm. B) Two weeks postoperatively. Pronounced fibrosis (C) and new bone formation (B) almost obliterate sinus cavity (S). Note that epithelial lining is missing. Bar — 1,000 µm.

no sign of clinical infection.

As early as 1 week postoperatively, most of the denuded sinus lining was found to have been reepithelialized by a poorly differentiated epithelium, although a few ciliated cells could be discerned. The lamina propria consisted of numerous inflammatory cells, fibroblasts, and newly formed vessels (Fig 3A). However, areas of ulceration could still be detected up to 2 weeks postoperatively. After 2 weeks a further differentiation toward a ciliated epithelium took place. In the lamina propria the fibroblasts and collagen became more readily discernible (Fig 3B). At 1 to 2 months the sinus was lined by an epithelium similar to that of the normal mucosa, although areas of squamous cells were still encountered (Fig 3C). The lamina propria showed a marked fibrosis from 3 to 4 months (Fig 3D). A few goblet cells could be seen at this time. At 6 and 9 months postoperatively the epithelium had a normal structure. The subepithelial glands did not regenerate at any time throughout the study.

After 1 week, new bone formation could be visualized with osteoid and palisades of osteoblasts (Fig 4A). Furthermore, increased osteoclast activity was also evident during this period. In one animal, bone formation was most pronounced after 2 weeks, and the sinus cavity was almost completely obliterated by fibrosis and newly formed bone trabecules (Fig 4B). After 1 month, activated osteoblasts could still be found within certain parts of the section, and apposition of osteoid could be documented. The sinus cavities appeared diminished in size compared with contralateral controls. However, after 2 months and subsequently, no obvious bone activity could be detected.

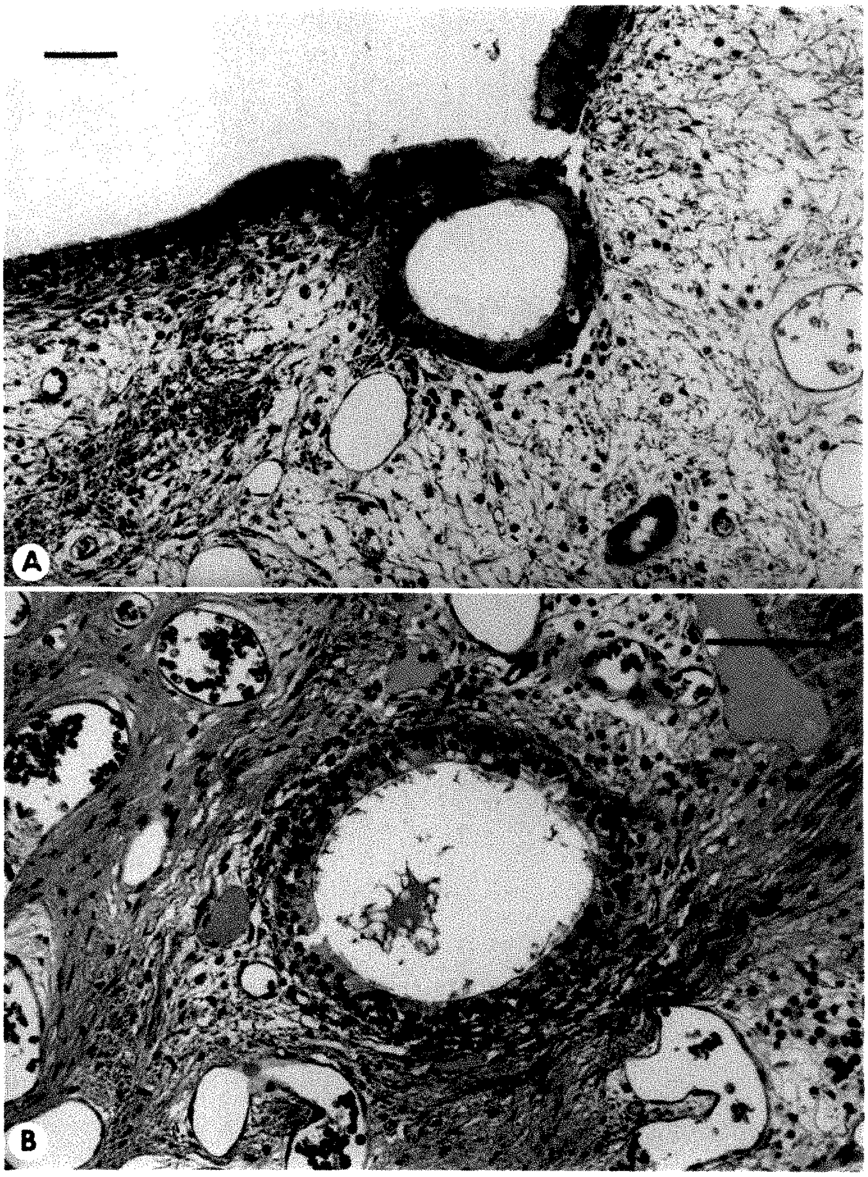

Fig 5. Bars — 100 μm. A) Two weeks postoperatively. Cystic formation ("atypical gland") is lined by respiratory epithelium. B) Four months postoperatively. Atypical gland.

Small mucosal polyps and mucosal invaginations could be found within the regenerated mucosal area. The invaginations appeared as small cystic formations ("atypical glands") within the lamina propria and could be encountered during all periods (Fig 5). Polyps were found mainly at 1 and 2 weeks after operation and were characterized by a reactive proliferation of connective tissue cells, including a deep inflammatory reaction (Fig 6).

Goblet cells are usually not present in the normal sinus mucosa of the rabbit. After operative removal of the mucosa, goblet cells developed within the remaining nonoperated epithelium, as well as in the regenerated epithelium. However, the cells were generally very sparse.

DISCUSSION

Appreciable differences have been reported in the time required for wound healing to take place after different types of respiratory mucosal damage. Not only differences in the extent and depth of trauma, animal species, age of animal, and level of the airway affected, but also the criteria used in judging the degree of recovery, may to some extent explain the disparate results reported.[16]

The healing process is complex. However, irrespective of what has caused the wound or tissue lesion, the sequence of events is fairly uniform. In the case of mucous membranes, there is general agreement that four or five different responses on the part of the epithelium itself are operative during regeneration: migration from adjacent epithelium, multiplication of undifferentiated cells, reorientation, and differentiation.[17] Migration of new cells from the undamaged areas starts within a few hours,[18] with an estimated velocity of 4 to 20 μm per hour in the

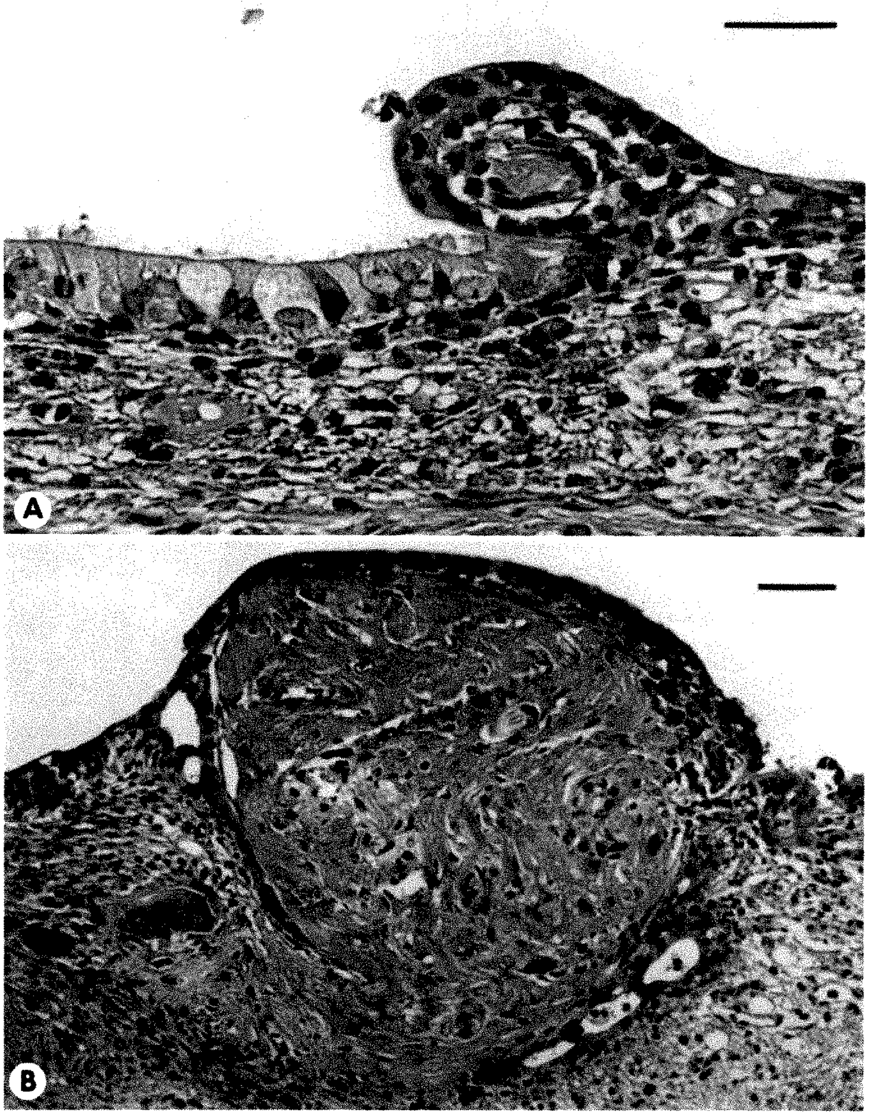

Fig 6. One week postoperatively. A) Polypous formation in epithelium. Bar — 30 μm. B) Early polyp formation. Note undifferentiated cells forming "microcavities" and splitting of polyp. Bar — 100 μm.

sinuses.[19] In regeneration, undifferentiated basal cells from adjacent untraumatized areas seem to serve as the main source of new cells. Inayama et al[20] have recently reported that 1 week after a cell suspension containing 94% basal cells was inoculated into denuded tracheal grafts, the basal cells had reestablished a continuous epithelial sheet, which after 2 to 4 weeks showed a typical mucociliary differentiation. The data of Inayama et al indicate that the basal cells are the main stem cells of the large airways, although in contrast, Evans et al[21] concluded that the nonciliated columnar secretory cells are the primary progenitor of other epithelial cells in the conducting airways. Most likely the basal cells also constitute the stem cells of the sinus mucosa. The basal cells of the sinus mucosa have, moreover, been shown to have a multipotency to differentiate into squamous cells, as well as ciliated or goblet cells, when isografted to other locations.[9]

Fibrosis was a prominent finding in the operated sinuses in the present investigation. The serous glands in the lamina propria were largely replaced by scar tissue. Thus, the remodeling and/or redifferentiation process of wound healing is not complete in the rabbit maxillary sinus after operative removal of the mucosal lining, at least as regards the lamina propria. Lactate accumulation, following tissue hypoxia occurring in a lesion with edema and increased density of the extracellular space, is a factor that induces angiogenesis and activates fibroblasts.[22] Moreover, it is thought that next to macrophages, fibroblasts function best at a low P_{O2}, probably because they are better adapted enzymatically to the lactate-rich environment of the inflammatory lesion.[23] Low P_{O2} and enhanced lactate concentrations are characteristic features of inflammatory sinus disease.[24] Consequently, the fibrosis may be even more pronounced after removal of diseased sinus mucosa, compared with the findings presented here, which were obtained in healthy tissue.

Gorham and Bacher[7] made macroscopic and microscopic observations on the maxillary sinus mucosa of patients operated on with a modified Caldwell-Luc technique. They concluded that a complete regeneration of the antral lining, including the ciliated columnar epithelium, is the rule following removal of the original membrane at the time of operation. In the dog, the time for complete regeneration of the maxillary sinus mucosa — including glands — is 3 to 5 months.[6] On the other hand, Hilding[8,25] observed that total experimental desquamation of the frontal sinuses in the dog usually led to obliteration of the sinus by scar tissue, and the same end result has been observed following desquamation of the sinus epithelium by acute viral infection.[26] Benninger et al[10] concluded that the restoration of the rabbit maxillary sinus mucosa cannot be regarded as complete after 2 months, since at this time various degrees of acute and chronic inflammation, fibrosis, and ulceration are present. Hosemann et al[19] studied regenerated sinus mucosa in rabbits up to 12 days. After standardized circular wounds were inflicted, the mucosa regenerated concentrically. Consistent with the findings of the present study, the subepithelial glands did not regenerate.

In the present study, apposition of new bone matrix was most pronounced during the first weeks after operative removal of the sinus mucosa, after which the osteoblast activity gradually declined. New bone formation has been described during the early stages of experimental anaerobic infections, eg, otitis media in the guinea pig[27] and maxillary sinusitis in the rabbit.[28] Hilding[25] reported that removal of the mucoperiosteum of the frontal sinus in the dog resulted in complete obliteration of the cavity. Furthermore, in an extended study, Hilding and Banovetz[29] reported that the new bone originated from the denuded bone itself, as well as from adjacent mucoperiosteum, and replaced connective scar tissue. Recently, Hosemann et al[19] showed that when the rabbit maxillary sinus was denuded of periosteum, a rapid regeneration of the surface epithelium was effected and reduced the rate of osteoneogenesis. Furthermore, systemically administered prednisolone reduced osteoblast activity, as did locally applied cortisone. This early bone formation is consistent with the findings reported here, as bone neogenesis was seen mainly at 1 and 2 weeks.

Structural abnormalities within the sinus thus remain after operative removal of the mucosa, and probably interfere with the normal function of the sinus, ie, mucociliary clearance. Recently, Kennedy and Shaalan[11] reported on impaired mucociliary clearance of the maxillary sinus in rabbits subjected to radical mucosal removal. The present study was designed to study the morphology of the regenerated sinus mucosa, and it was found that the "new" mucosal lining displayed a markedly reduced number of subepithelial glands. Future physiologic studies will reveal whether these structural changes influence physiologic characteristics such as mucociliary clearance and blood flow in the sinus.

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ANIMAL MODEL FOR PERSISTENT TYMPANIC MEMBRANE PERFORATIONS

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Topically applied hydrocortisone was used to develop an animal model for persistent tympanic membrane (TM) perforations. Hydrocortisone suspension was applied on the margins of TM perforations of standardized size in rats once daily for 10 days. The healing patterns of the TMs were mapped weekly and, when the perforations were about to close, daily. After 50 days, all hydrocortisone-treated perforations were open, whereas the controls closed within 9 to 12 days. At 3 months, when one third of the perforations still were open, the TMs were studied by otomicroscopy and light microscopy. All TMs were thickened and covered by keratin and wax. The thickened epidermal layer at the border of the TM perforations that remained open also draped the surface of the perforation facing the middle ear cavity. The thickened connective tissue layer contained abundant fibroblasts with their axes of length oriented at random. Both application of 1.4% hyaluronan and wounding of the perforation border enhanced the healing rate of the hydrocortisone-induced chronic TM perforation.

KEY WORDS — animal model, chronic otitis media, chronic perforation, healing, rat, tympanic membrane.

INTRODUCTION

A perforation of the tympanic membrane (TM) causes hearing loss of various degrees depending on the size and location of the perforated area. Moreover, a perforation of the TM constitutes a permanent threat of reinfection, either from contamination from the external canal or by migration of secretions from the nasopharynx, the latter as a consequence of the altered aerodynamics of the tubotympanic cleft.

Clinically, a permanent TM perforation is defined as a hole in the TM that still persists after a certain period of time, usually 2 months. Apart from trauma, most permanent TM perforations are the sequela of acute otitis media during childhood, or otitis media with effusion. This condition usually proceeds to chronic otorrhea, hence the term chronic otitis media.[1] The mechanism by which this process occurs is not well understood.

To reduce the complications connected with a permanent TM perforation, attempts to close this perforation should be performed. So far, this has been achieved by surgical techniques (myringoplasty). However, other methods, including topical treatment with substances with wound-healing properties, have also been suggested.[2] Obviously, to test such substances, an animal model for chronic perforations is a prerequisite.

Recently, Spandow et al[3] demonstrated that hydrocortisone, topically applied in the middle ear through a perforated TM, delayed the spontaneous tissue repair of TM perforations. In the present study, a similar approach is used to create a model with a persistent, noninfected TM perforation. This TM perforation model can be used for future investigations of TM repair and also for studies of the mechanisms involved in a condition resembling chronic otitis media.

MATERIALS AND METHODS

Experiment 1. Sixteen healthy adult male Sprague-Dawley rats, weighing 300 g, were used for development of a chronic TM perforation. The animals were anesthetized by a barbiturate through a tail vein, and TM perforations were performed bilaterally with a myringotomy lancet through the external auditory

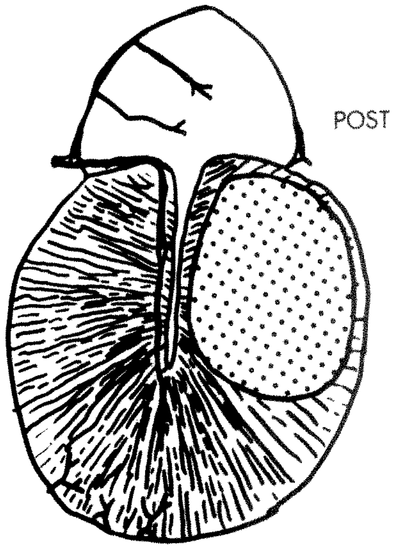

Fig 1. Schematic drawing of left tympanic membrane from rat. Perforated area (dotted) in upper posterior quadrant is indicated. (Reprinted with permission.[3])

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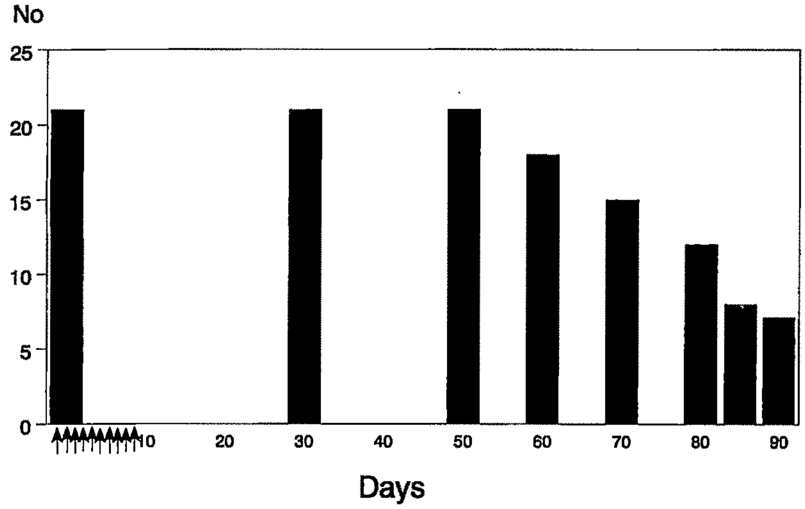

Fig 2. Experiment 1. Number of open tympanic membrane perforations throughout study.

canal, under sterile conditions. The perforations were standardized in size and engaged the whole upper posterior quadrant (Fig 1). The animals were divided into 3 groups. Group 1 (8 animals) had both their ears exposed to the hydrocortisone suspension. Group 2 (5 animals) had the right ears subjected to hydrocortisone and the left ears to sterile water. In group 3 (3 animals), all ears were exposed to sterile water only. The border of the TM perforation was exposed to approximately 20 µL of either a 2% hydrocortisone suspension micronized in sterile water, or sterile water only, once every day for 10 days. Excess substance was left in the middle ear and in the ear canal.

By otomicroscopy the healing pattern of the TM perforation was mapped weekly for a 3-month period and documented with photographs. At the end of the 3-month period, the animals were painlessly sacrificed with an overdose of barbiturate and decapitation. The tympanic bulla was dissected free, and through a hole in the bulla a fixative containing 3% glutaraldehyde in 0.1 mol/L sodium cacodylate buffer with 4% polyvinylpyrrolidone added was instilled into the middle ear cavity. The heads were kept in the fixative for at least 24 hours. After fixation the TMs were dissected, rinsed in buffer, then postfixed in 1% osmium tetroxide in cacodylate buffer. After dehydration in increasing concentrations of ethanol, the specimens were embedded in Epon. Semithin sections were cut through the perforated area, perpendicular to the handle of the malleus, on a Porter-Blum ultramicrotome, stained with toluidine blue, and examined in a light microscope.

Experiment 2. To test the utility of the chronic perforation model, a persistent TM perforation was created bilaterally in 15 animals as described above. Three weeks after the last application of hydrocortisone, ears with the TM perforation still open (27 ears) were divided into 4 groups at random. In group I (5 ears), the TMs were mechanically wounded in the perforation border. In group II (6 ears), the TMs were exposed to topically applied exogenous 1.4% hyaluronan (Kabi-Pharmacia, Uppsala, Sweden). In group III (8 ears), the TMs were treated with a combination of wounding and 1.4% hyaluronan. In group IV (8 ears), the TMs were left untouched and served as controls.

The healing pattern and time for closure of the TM perforations were mapped weekly, and when the perforations were about to close, daily. At 3 months after the start of the experiment, the TMs were prepared for light microscopy according to the procedure described above.

RESULTS

Experiment 1. All 21 TM perforations exposed to hydrocortisone suspension in groups 1 and 2 remained open at 1 month, as well as after 50 days (Fig 2). Three perforations had closed by day 60, 3 more by day 70, and another 3 by day 80. By day 90, 5 perforations still were clearly visible. In 7 ears the TM status could not be mapped, as the TMs were covered by wax; however, 2 of these specimens were not closed when evaluated in the light microscope. Hence, 7, or one third, of the perforations were open at the end of the 3-month period.

The TM perforations exposed to hydrocortisone were all covered by keratin and wax (Fig 3). Within the perforation edge the collagen was organized in densely packed masses with abundant fibroblasts intermingled. The fibroblasts' long axes were randomly oriented. The epidermis was thickened and also reached the surface of the perforation facing the middle ear cavity. The mucocutaneous junction was

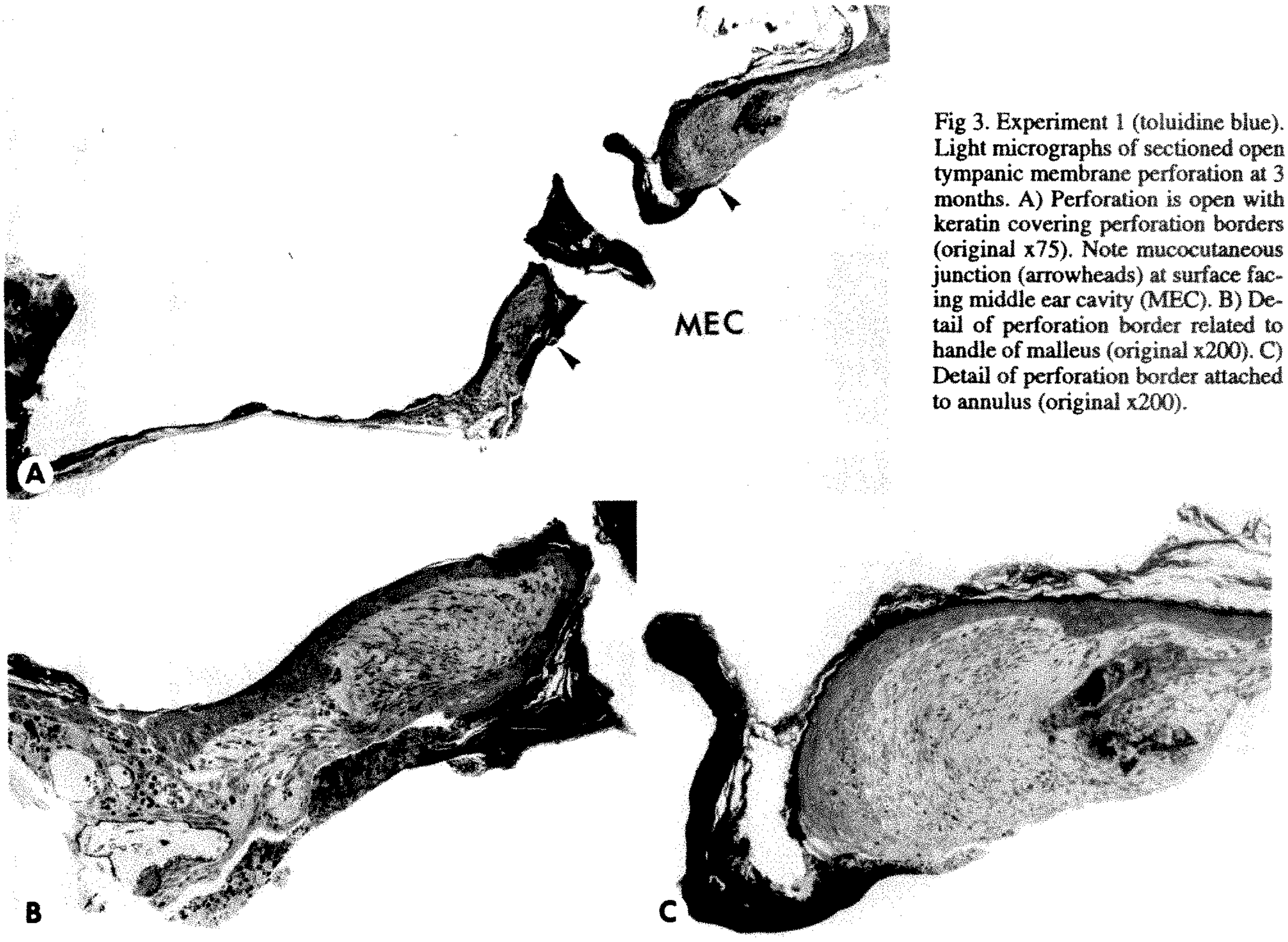

Fig 3. Experiment 1 (toluidine blue). Light micrographs of sectioned open tympanic membrane perforation at 3 months. A) Perforation is open with keratin covering perforation borders (original x75). Note mucocutaneous junction (arrowheads) at surface facing middle ear cavity (MEC). B) Detail of perforation border related to handle of malleus (original x200). C) Detail of perforation border attached to annulus (original x200).

thus located on the inner surface of the TM.

The healed areas of the earlier perforated TMs (Fig 4) were all considerably thickened — about 5 to 10 times. This thickening was related to the connective tissue layer, which also contained inclusions of a bonelike material. The epidermis was markedly thin.

The sterile water–treated TM perforations in group 3 were all healed within 9 to 12 days, whereas those in group 2 closed between days 12 and 17. The TMs were thin and resembled those that heal spontaneously. Hence, the TMs showed only a minor thickening of the connective tissue layer.

Experiment 2. The results from the treatment test in the chronic perforation model are shown in Fig 5. Of the initial 27 open TM perforations, 9 remained open at the end of the 3-month period. Interestingly, 5 of these were controls and not touched. Only 4 of the 19 treated TMs were open. In all, 15 TM perforations (79%) were closed after treatment with hyaluronan or wounding, in contrast to the controls, of which only 3 of 8 (37%) were healed. Figure 5 also demonstrates that hyaluronan accelerated the healing process in a striking manner. The majority of perforated TMs treated with hyaluronan alone or in combination with wounding closed within a few days after the treatment procedure, whereas the TM perforations in the group treated only by wounding healed 30 to 50 days later.

DISCUSSION

Healing of TM perforations has been extensively studied[4-6] and shows that migration of the keratinizing squamous epithelium is a prerequisite for closure of the TM perforation. Most acute TM perforations, which involve traumatized but fresh tissue, both in animals and humans, will heal spontaneously and thus do not fulfil the criteria for studies of chronic perforation.

The present study showed that hydrocortisone topically applied to a perforated TM markedly retarded the healing process. Most perforations were covered by keratin and wax, and the mucocutaneous junction was located on the inner TM surface facing the middle ear cavity. It seemed that the movement of the keratin layer, which to a great extent moves in a centrifugal direction from the umbo to cover the perforation, was arrested. The appearance of the hydrocortisone-treated perforated TMs in many respects resembled the TMs of patients with chronic

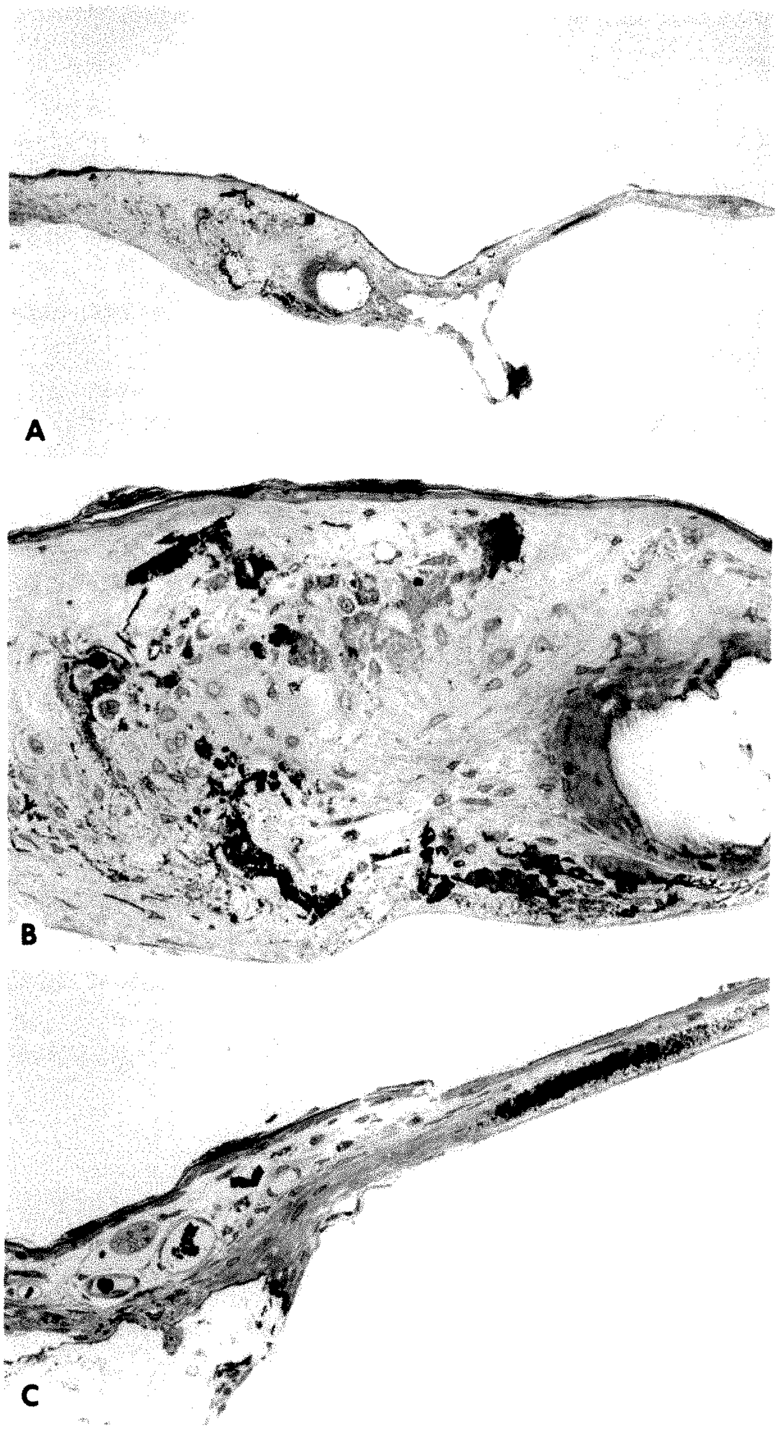

Fig 4. Experiment 1 (toluidine blue). Light micrographs of sectioned closed tympanic membrane (TM) perforation at 3 months. A) Healed area is considerably thickened (original x120). Connective tissue contains bonelike material. B) Detail of perforated posterior portion of TM (original x500). C) Detail of intact anterior portion of TM (original x500).

otitis media. In the control group (group 3), the perforation closed spontaneously within 12 days in accordance with earlier studies.[7] In contrast, control ears in animals that had their contralateral ears exposed to hydrocortisone showed delayed healing but closed within 17 days. The delayed healing rate in these sterile water–treated ears is most probably caused by systemic glucocorticoids originating from the contralateral ear after swallowing.

Glucocorticoids are commonly prescribed in dermatologic practice. Long-term treatment with cortisone on skin exerts profound effects on several connective tissue components, eg, collagen, elastin, glycosaminoglycans, and fibronectin.[8] In corticosteroid-induced atrophy of human skin[9] a flattening of the dermoepidermal junction has been shown. Furthermore, glucocorticoids have the capacity to reduce the synthesis of hyaluronan (hyaluronic acid), one of the major components of the connective tissue matrix.[10,11] Suppression of hyaluronan synthesis by

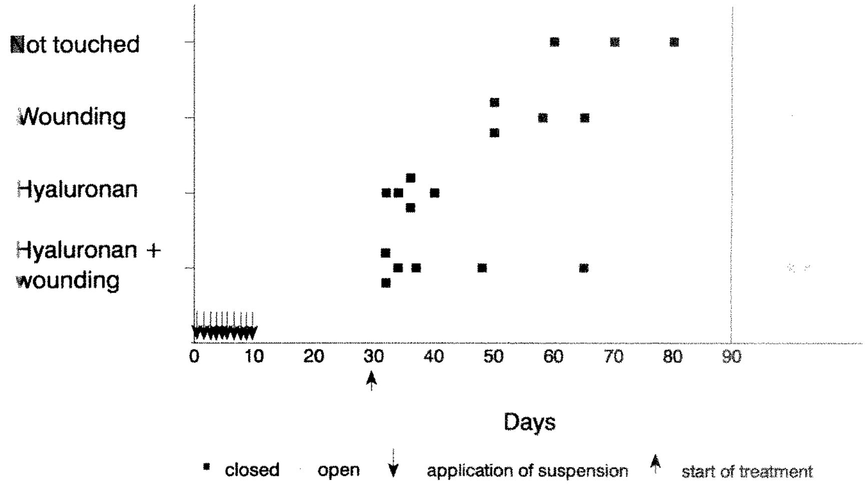

Fig 5. Experiment 2. Otomicroscopic evaluation of closure rate of chronic tympanic membrane perforations after various treatments.

the application of hydrocortisone could be one possible mechanism to explain the delayed healing of the perforated TM. Topical application of hyaluronan onto experimental acute perforations has been shown to enhance the healing rate[12,13] and to improve the quality and the restoration of the fibrous connective tissue layer of the scar area.[14] Interestingly, the present study showed hyaluronan to markedly accelerate the healing process of the hydrocortisone-induced chronic perforation.

In a perforated TM the proliferating keratinized epithelium has to bridge the gap of the TM prior to the development of a bed of granulation tissue. This contrasts with the healing process of wounds in other parts of the body, in which the migrating epithelium is normally guided and supported by a preceding spur of keratin. Persistent TM perforations in the clinic have traditionally been covered by a thin paper patch after wounding of the perforation borders. The wounding removes keratin and stratified epithelium from the surface of the perforation border facing the middle ear cavity. Demolition or "peeling" of this barrier may create an inflammation and per se act as a stimulus for healing-promoting factors in the connective tissue layer, such as epithelial growth factor. Wounding of the perforation border in the present model in a similar manner increased the healing rate compared to that in the untouched controls.

An animal model for a chronic TM perforation could be of great value in elucidating the role of synthetic biomembranes and growth-accelerating substances such as epithelial growth factor in an attempt to develop a simple technique for the repair of chronic noninfected TM perforations.

Few animal models of TM chronic perforations have been described in the literature. Amoils et al[15] recently reported a model for chronic TM perforation in chinchillas. A thermally inflicted myringectomy followed by medial infolding of the TM microflaps created a permanent perforation that remained open in 84% of cases after 6 to 8 weeks.

CONCLUSION

Our study presents an animal model for a persistent TM perforation. All experimental TM perforations with application of hydrocortisone remained open after 50 days, in contrast to acute TM perforation, which healed spontaneously within 9 to 12 days. The TM perforations, standardized in size, were easy to perform, and the TM can be evaluated by otomicroscopy. An in vivo model for chronic TM perforations can be used not only for studying the pattern of wound healing, but also for the assessment of methods to improve TM repair. Furthermore, the hydrocortisone-induced chronic perforation model might be useful in studying mechanisms of chronic otitis media.

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THIRD INTERNATIONAL SYMPOSIUM ON MENIERE'S DISEASE

The Third International Symposium on Meniere's Disease will be held October 20-23, 1993, in Rome, Italy. For information, contact Kugler Publications bv, Congress Department, PO Box 1498, New York, NY 10009-9998; telephone (212) 477-1970; fax (212) 477-0181.

FUNCTIONAL ENDOSCOPIC SINUS TECHNIQUES

A course on functional endoscopic sinus techniques will be held in Graz, Austria, July 1-3, 1993. It will be conducted in German. For further information, contact Prof Dr Heinz Stammberger, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; telephone 43 316 385 3448; fax 43 316 385 3425.

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IMAGING CASE STUDY OF THE MONTH

MAGNETIC RESONANCE IMAGING OF BILATERAL FAMILIAL PARAGANGLIOMAS

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Paragangliomas, also known as chemodectomas or glomus tumors, arise from nonchromaffin paraganglia or glomus bodies.[1] They may be unilateral, bilateral, or multicentric, although they are more commonly associated with a glomus tumor in another location. Paragangliomas also have a familial distribution indicating a hereditary pattern that appears to be autosomal dominant.

We report two Turkish brothers with bilateral paragangliomas whose clinical symptoms manifested at the age of 17 years and progressed in a similar manner.

CASE REPORT

Two Turkish brothers, 19 and 25 years of age, presented with a history of progressively enlarging neck masses with gradual loss of hearing that started at the age of 17 years in both. The older brother had bilateral deafness at the age of 21 years, and the younger brother had left-sided deafness at the age of 19 years. There was no family history of paragangliomas. Computed tomography (CT) of the younger brother revealed bilateral enhancing masses, with the left mass causing widening of the jugular fossa and erosion of the temporal bone, as well as involvement of the middle and posterior fossa structures. In the older brother, CT revealed large bilateral enhancing masses causing widening and destruction of the jugular fossa and cranial base, with involvement of the middle and posterior fossa structures. Before the evaluation at Ankara Oncology Hospital, biopsies of the lesions were performed elsewhere without the advantage of the above CT findings. Pathologic findings were consistent with paraganglioma in both patients.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) of the younger brother showed a large left jugular fossa mass with bone erosion, as well as middle and posterior fossa involvement, and a small mass in the right jugular area (Fig 1). In the older brother, MRI showed large bilateral masses that eroded the jugular fossa, temporal bone, and cranial base and invaded the middle and posterior fossae. The brain stem and fourth ventricle were displaced to the right, creating an obstructive hydrocephalus (Fig 2). The T1-weighted images of both brothers showed isointense masses with signal void and hyperintense areas consistent with highly vascularized or vascular tumors. The T2-weighted images of both showed hypointense masses with signal void and hyperintense areas that gave the paragangliomas a characteristic "salt and pepper" appearance. Radiotherapy was carried out on both patients. Unfortunately, the patients were not available for follow-up evaluation.

DISCUSSION

Glomus bodies are small nodules, up to 1.5 mm in diameter, of capillary and precapillary blood vessels interspersed with epithelioid cells. They are located typically in adventitia of the dome of the jugular bulb, along the course of the tympanic branch of the glossopharyngeal nerve from the jugular fossa to the promontory in the middle ear, and along the course of the auricular branch of the vagus nerve, which passes from the jugular fossa to the descending portion of the facial nerve.[2] Tumors arising from the glomus bodies may develop in any location in which these cells exist, from the central nervous system to the femoral arteries.[2]

Paragangliomas are the most common tumor of the temporal bone.[2] They are classified by location: those from the jugular fossa are called glomus jugulare tumors, and those from the region of the middle ear

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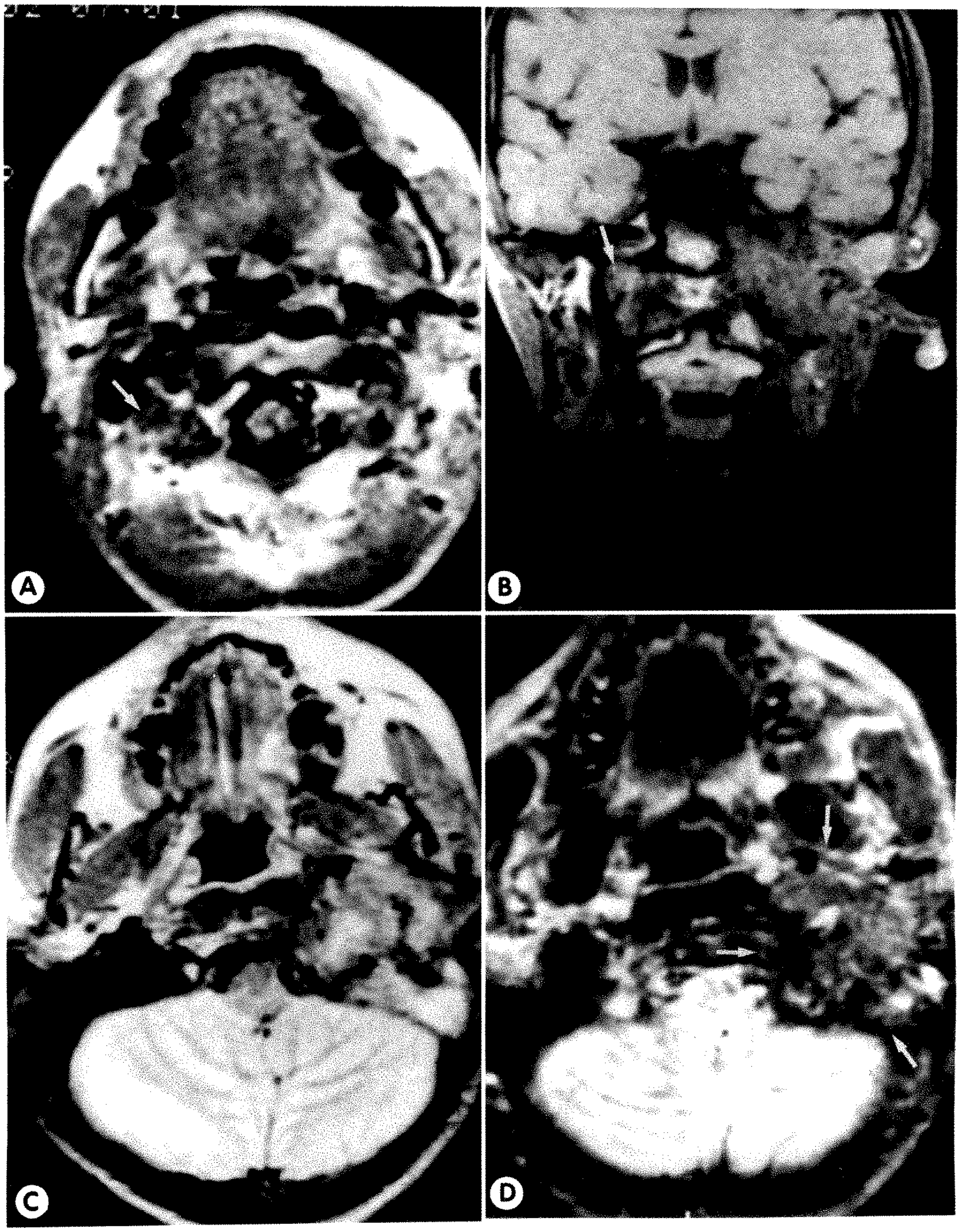

Fig 1. Magnetic resonance images of younger brother. A,B) T1-weighted (TR/TE/NEX = 350/30/1) images show large isointense mass on left side (B) and small mass (arrows on A and B) on right side of neck. Mass on left side has eroded into jugular fossa and cranial base and has invaded temporal and posterior fossae medially and skin laterally. These masses are isointense on C) proton density (2,000/30/2) and D) T2-weighted (2,000/90/2) images. Both masses have signal void areas, which are characteristic of highly vascularized tumor and/or tumor of vascular origin. Arrows on D — left-sided mass.

are called glomus tympanicum tumors. They vary in size from several millimeters to several centimeters. Precapillary arteriovenous shunts and nonchromaffin cells are the histologic characteristics of paragangliomas. Generally, these tumors are histologically benign and exhibit slow progression and nonmetastatic growth, although metastatic spread has been reported.[3,4] Their clinical manifestations result from expansion into areas around the site of origin. The growth characteristics of these tumors were described by Phelps and Stansbie[2] in 1988. Anatomically, the bony plate forming the dome of the jugular bulb is very thin. Paragangliomas located in this region may expand through the middle and posterior fossae by

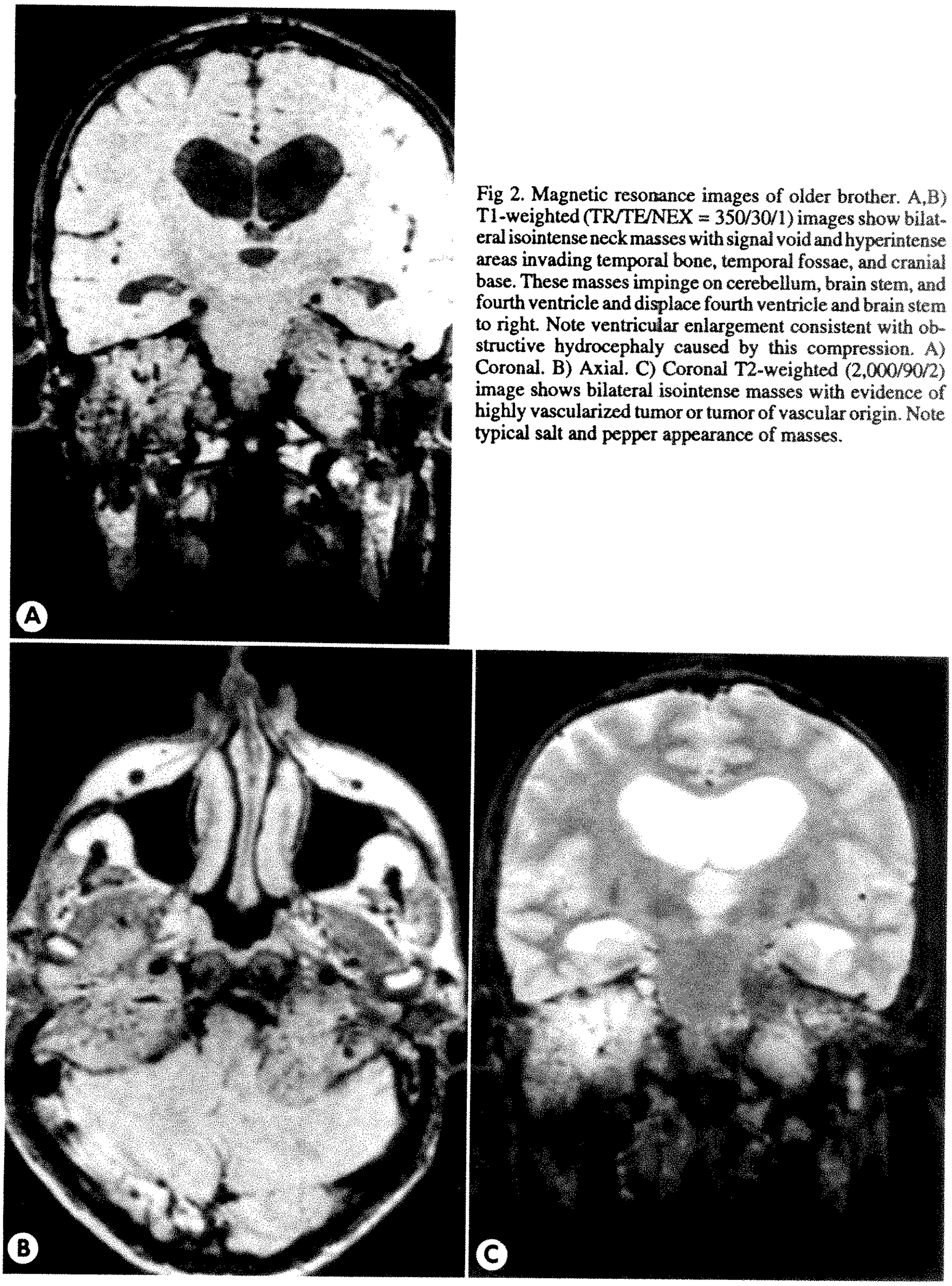

Fig 2. Magnetic resonance images of older brother. A,B) T1-weighted (TR/TE/NEX = 350/30/1) images show bilateral isointense neck masses with signal void and hyperintense areas invading temporal bone, temporal fossae, and cranial base. These masses impinge on cerebellum, brain stem, and fourth ventricle and displace fourth ventricle and brain stem to right. Note ventricular enlargement consistent with obstructive hydrocephaly caused by this compression. A) Coronal. B) Axial. C) Coronal T2-weighted (2,000/90/2) image shows bilateral isointense masses with evidence of highly vascularized tumor or tumor of vascular origin. Note typical salt and pepper appearance of masses.

eroding this thin bony structure of the middle ear floor. Expansion to the cranial base and posterior fossa causes a wide range of symptoms related to the expansion and displacement, including paralysis of the 7th, 9th, and 11th cranial nerves. Patients with jugular bulb tumors (glomus jugulare) generally have neck masses with lower cranial nerve symptoms, whereas patients with tumors located in the middle ear (glomus tympanicum) have tinnitus, pulsation, vertigo, and loss of hearing or deafness as the presenting symptoms. Our cases showed bilateral and unilateral large, progressively growing neck masses with gradual loss of hearing that started at the age of 17 years. The older brother had bilateral deafness at the age of 21 years, and the younger brother had left-sided deafness at the age of 19.

Epidemiologic studies suggest that there are two forms of paragangliomas. The most common is the sporadic form, in which there is a 5% incidence of multiple tumors. The familial form accounts for 7% to 10% of paragangliomas in the head and neck.[5,6] Multiple paragangliomas occur in approximately 25% to 35% of the familial cases. Bilateral involvement is reported in about 25% of familial cases, compared with a 2.8% occurrence in nonfamilial cases. It has been suggested that the familial form manifests itself at a younger age. The inheritance pattern of the familial type of head and neck paragangliomas appears to be autosomal dominant, with variable penetrance and expressivity.[5] However, the development of these tumors is not caused solely by the inherited gene(s). An additional event that is still unclear is necessary, presumably at the somatic cell level. Even though the grandparents, parents, and other siblings were clinically free of the disease, bilateral involvement in both of our cases is supporting evidence for the familial type. Furthermore, the progression of the masses, with middle and posterior fossa involvement, and onset at a younger age also support the familial pattern in these cases. We think that the similarity in age at onset of symptoms also is further supporting evidence that our cases are the familial type, even though there is no family history.

Magnetic resonance (MR) appears to be the imaging modality of choice in the evaluation of paragangliomas, because of better soft tissue contrast and soft tissue-bone differentiation with lack of bony artifact, as well as the possibility of multiplanar imaging with flow phenomenon. In the conventional spin-echo technique, blood flow has a flow void appearance that distinguishes the vessel from the surrounding tissue. Thin slices and surface coils with different parameters obtain better signal to noise ratios, and developing fast-scan techniques demonstrate even small tumors in the vessels. Gadolinium-enhanced MRI, particularly dynamic MRI, is very helpful in demonstrating the smaller tumors.[4] The maximum signal intensity increment in the tumoral tissue has been detected 150 seconds after injection. After this peak, the intensity diminishes gradually because of the washout effect of the highly vascularized tumor tissue.[4] Noninvasive, sensitive, and reliable, MRI should be the first imaging modality used in screening other family members with suspected small asymptomatic paragangliomas. The role of MRI and/or MR angiography is also important in the follow-up and evaluation of the response to therapy.

Our cases showed the MR characteristics of a highly vascularized tumor or a tumor of vascular origin: 1) signal void areas that correspond to rapidly flowing blood or hemosiderin deposits and 2) hyperintense areas that correspond to slow-flowing blood or thrombus. Both cases had a salt and pepper appearance on T2-weighted images, which is further evidence for a vascular origin. The soft tissue masses of both cases had irregular margins, and caused erosion of both jugular fossae, the cranial base, and the temporal bone. One of the cases showed bilateral and the other showed left-sided extensive posterior and middle fossa involvement through this erosion. The bilateral involvement of the middle and posterior fossae also caused obstructive hydrocephalus and related symptoms by compressing and displacing the brain stem in the older brother. No postcontrast MR studies with gadolinium were performed. None of the other family members were evaluated by any screening method.

The treatment of choice remains controversial, ranging from surgery to radiotherapy to both. In glomus tympanicum and small glomus jugulare tumors without extensive involvement of the skull base, carotid artery, or multiple cranial nerves, surgery appears to be the treatment of choice.[7] Excellent control rates in more advanced and recurrent lesions have been reported with radiotherapy.[8] Moreover, because of the slow natural history of these tumors, the ultimate treatment outcome is difficult to evaluate unless long-term follow-up for 10 to 20 years is available. Because of tumor size and involvement of the middle and posterior fossae, only radiotherapy was performed in our cases. On examination after the treatment, the size of the masses had decreased, with some improvement in symptoms, particularly related to the hydrocephalus. Unfortunately, the patients were not available for further evaluation by CT or MRI.

Small asymptomatic paragangliomas in family members cannot be excluded without screening examinations, particularly MRI or MR angiography, even though these persons are clinically free of disease. Even though available data are not sufficient for genetic diagnosis, we think these cases show inheritance because of the initial symptoms, similar age at onset, bilaterality, and aggressive behavior and growth.

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6TH INTERNATIONAL CONGRESS ON INTERVENTIONAL ULTRASOUND

The 6th International Congress on Interventional Ultrasound will be held Sept 7-10, 1993, in Copenhagen, Denmark. For further information, contact Christian Noisse, Congress Secretary, Department of Ultrasound, Herley Hospital, University of Copenhagen, DK-2730 Herley, Denmark.

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THE DEAFNESS RESEARCH FOUNDATION
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IMAGING CASE STUDY OF THE MONTH

FACIAL NERVE NEUROMA

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INTRODUCTION

In a review of 600 temporal bone specimens, Saito and Baxter[1] found five facial neuromas; clinically, however, facial nerve neuromas are cited as being uncommon[2,3] or even rare.[4,5] Importantly, although early series such as that of Conley and Janecka[6] emphasized the infrequency with which the diagnosis was correctly established preoperatively, modern imaging modalities have vastly improved diagnostic acumen and have assisted surgical planning by appropriately delineating the extent of tumor.

CASE REPORT

A 19-year-old man noted a left-sided progressive hearing loss of 3 years' duration. Although there was an associated sensation of aural fullness, there was no tinnitus, fluctuation in hearing, or infection. He denied xerophthalmia and dysgeusia. There was an associated, intermittent left lower facial twitch. Therapy, consisting of allergy injections, antibiotics, and tympanostomy tube insertion on two occasions, had not been beneficial.

On physical examination, the Weber was found to lateralize to the left and there was a negative Rinne on the left and a positive Rinne on the right. A slightly erythematous, nonpulsatile mass could be seen extending laterally through the tympanic membrane and occupying the medial 3 to 5 mm of the external auditory canal. Facial nerve function at rest was normal, with an intermittent left mental twitch. On vigorous facial movement, a slight weakness was noted involving all branches of the left facial nerve (House grade II).

Audiometric evaluation documented normal hearing on the right but a 50-dB conductive hearing loss on the left, with 100% discrimination.

High-resolution, non-contrast-enhanced tempo-

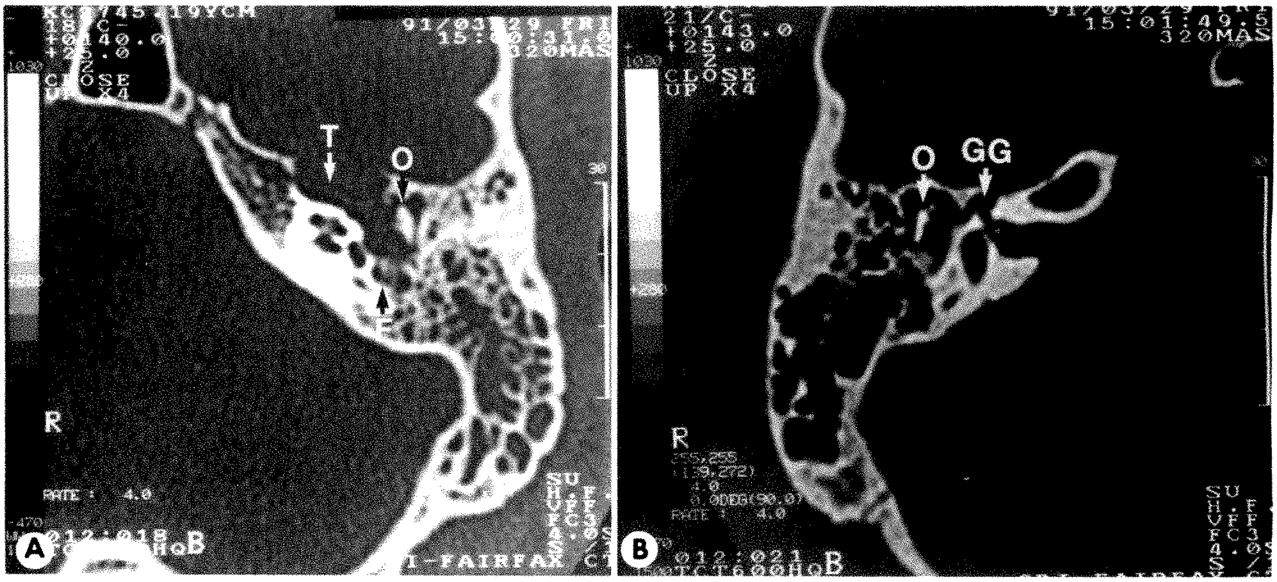

Fig 1. Axial temporal bone computed tomograms. A) Showing tumor (T) occupying left tympanic cavity and displacing ossicles (O) laterally. Fallopian canal (F) is expanded. B) Comparable image of right ear. Position of ossicles (O) can be noted, as well as normal configuration of geniculate ganglion (GG).

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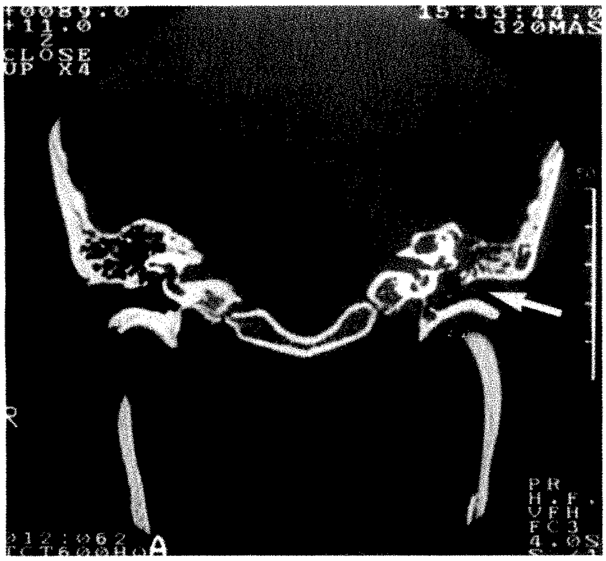

Fig 2. Coronal temporal bone computed tomogram showing tumor encroaching on external auditory canal on left (arrow); there also is erosion of tegmen.

ral bone computed tomography (CT) revealed a large soft tissue mass filling the tympanic cavity with lateral displacement of the ossicles (Fig 1), enlarging the vertical segment of the fallopian canal, eroding the tegmen, and occupying the external auditory canal (Fig 2). The mass followed the expected course of the facial nerve, and there were no "honeycomb" osseous changes in the region of the geniculate ganglion. Rather, the bone appeared to be sharply eroded in this region.

The mass displayed a low-intensity signal on T1-weighted magnetic resonance images, and a bright signal both with T2-weighted imaging and with gadolinium (Fig 3). A 2-cm middle cranial fossa extension occupied the region of tegmental erosion seen on CT (Fig 4).

Arteriography showed an avascular mass with no substantial cranial vessel displacement or compression.

A combined middle fossa–transmastoid exploration of the facial nerve revealed a facial nerve neuroma completely replacing the facial nerve from the lower portion of its vertical segment to the medial aspect of its internal auditory canal segment. The long process of the incus was destroyed, and the stapes crura, still attached to the stapedius tendon but separate from the footplate, were displaced toward the round window. Complete tumor removal was confirmed by frozen section control, both proximally and distally. Anastomosis of nerves VII and XII was performed.

Left-sided facial movement became evident at 3½ months postoperatively, associated with excellent resting tone (House grade IV).

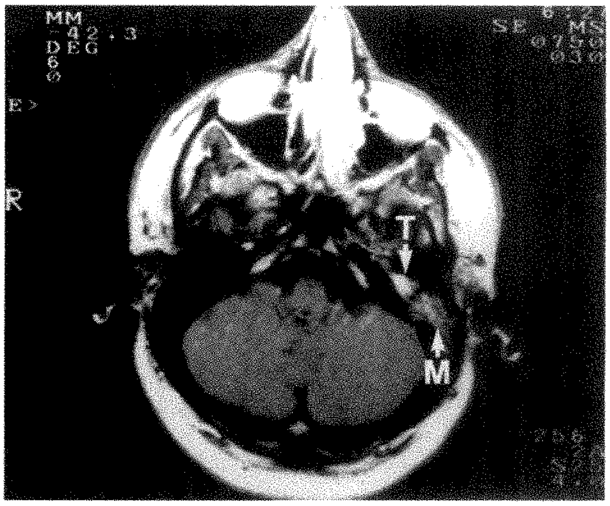

Fig 3. Axial, gadolinium-enhanced magnetic resonance image showing tumor (T) as enhancing area in tympanic cavity, while fluid in mastoid (M) air cells is visualized as area of lower intensity.

DISCUSSION

Facial nerve neuromas arise from the Schwann cell sheath of the facial nerve — more specifically, its sensory component.[1] They may be found anywhere along the course of the facial nerve, although the geniculate ganglion seems to have a predilection for involvement.[2]

There is no constellation of symptoms specific for facial nerve neuroma. Symptoms suggestive of a neoplasm involving the facial nerve include facial twitching, gradual facial paralysis, and recurrent facial paralysis.[7] O'Donoghue et al[8] reported that hearing loss and tinnitus were the most common presenting symptoms in their review of 48 patients with facial nerve neuromas. Tumor size exceeds expectations based on symptoms and clinical findings; thus, despite normal tearing and normal stapedius reflexes, both the geniculate ganglion and the distal facial nerve may be involved with tumor.

Diagnostic imaging, then, plays a key role in establishing the diagnosis and delineating tumor extent. The CT findings typical of facial nerve neuromas have been summarized by Inoue et al[4] and are consistent with the segmental fashion in which the facial nerve is involved. In common with facial nerve tumors in general, neuromas show destruction of the fallopian canal and constitute a soft tissue density in the tympanomastoid compartment; facial neuromas also may be associated with internal auditory canal widening, cerebellopontine angle extension, or a middle cranial fossa mass, mimicking vestibular schwannomas. Facial nerve neuromas enhance with contrast administration in a manner similar to vestibular schwannomas. Specific to facial neuromas, and serving to distinguish them from vestibular

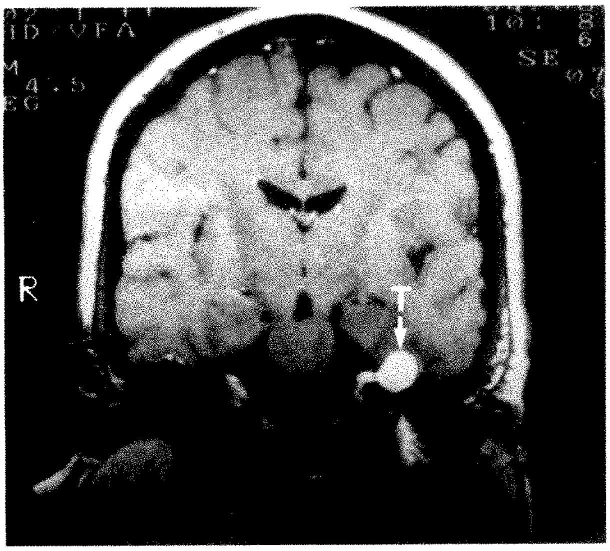

Fig 4. Coronal, gadolinium-enhanced magnetic resonance image, showing tumor (T) occupying middle cranial fossa, in correlation to area of tegmental erosion seen in Figs 1A and 2. Apparent "stalk" extending medially from tumor is marrow in petrous apex, not tumor.

schwannomas, are 1) enlargement of the labyrinthine segment of the facial nerve canal associated with a middle cranial fossa mass at the anterior surface of the middle portion of the petrous bone, and 2) erosion of the anterosuperior aspect of the internal auditory canal.[4]

The utility of gadolinium-enhanced magnetic resonance imaging in evaluating facial nerve neuromas has been emphasized by Parnes et al,[9] particularly with respect to determination of tumor extent, identification of clinically silent lesions, and differentiation from vestibular schwannomas. Gadolinium enhancement of the geniculate ganglion and distal facial nerve are findings that Parnes et al cite as being most useful in distinguishing a facial nerve neuroma from a vestibular schwannoma in a patient presenting with retrocochlear findings and an internal auditory canal or cerebellopontine angle mass.

Definitive management comprises surgical resection, but the timing of surgical intervention is dependent on the status of facial nerve function and/or the development of an intracranial mass lesion. Small tumors, with minimal impairment of facial nerve function, may be followed by serial imaging studies. The development of an intracranial mass or facial paralysis strengthens consideration of surgical management. As the true extent of tumor does not correlate with observed neural distention, frozen section margins are recommended to ensure complete tumor removal.[2] Diagnostic imaging assists in surgical planning for the exposure necessary to remove the tumor. Although with small tumors some normal facial nerve fibers may remain and may be preserved with surgical excision of the tumor, with larger tumors the facial nerve cannot be preserved and facial reanimation must be accomplished, whether by end-to-end anastomosis after mobilization, interposition nerve grafting, or crossover procedures, such as the facial-hypoglossal nerve anastomosis.

SUMMARY

Facial nerve neuromas are an unusual cause of facial nerve dysfunction and hearing loss. As clinical manifestations do not accurately reflect tumor extent, imaging techniques can greatly assist the clinician in appropriate diagnostic evaluation and management.

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PATHOLOGY CONSULTATION

TUMEFACTIVE FIBROINFLAMMATORY LESIONS OF THE HEAD AND NECK

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Tumefactive fibroinflammatory lesions of the head and neck are idiopathic, histologically benign, tumor-forming lesions that clinically simulate malignancies. Their histopathologic appearance is nearly identical to that of fibrosclerotic lesions of the mediastinum and retroperitoneum and Riedel's thyroiditis, and in some cases, a congeneric (periarteritis) origin is postulated. There is no optimum treatment, and recurrence and persistence are common. The suggested initial treatment is corticosteroid administration.

In 1975 Rice et al[1] described a histologically benign yet clinically aggressive fibrosclerotic lesion in the soft tissues of the neck, which they considered to be the homologue of sclerosing mediastinitis and peritonitis, and called it sclerosing cervicitis.

Histologically identical lesions were subsequently reported to arise in head and neck sites other than the soft tissues of the neck (orbit, sinonasal tract, face, base of tongue, parotid gland, and periparotid soft tissues).[2-6] In order to accommodate the diversity of involved sites other than the neck, the term tumefactive fibroinflammatory lesion of the head and neck is now most often used for clinicopathologic diagnosis.[3,4]

The fibrosclerotic lesions in the head and neck are believed to be part of a broader fibrosclerosing syndrome that includes Riedel's thyroiditis and idiopathic sclerosing (fibrosing) mediastinitis, retroperitonitis, and cholangitis.[1,4,7] Inclusion of all these lesions in the syndrome implies a common causation and pathogenesis that is unproven and probably unlikely. Even the suggested diagnostic terminology of tumefactive fibroinflammatory lesion of the head and neck is unsatisfactory, since its misuse allows the inclusion of a variety of unrelated fibroproliferative lesions. In that respect, only the fibrosclerotic lesions in the soft tissues of the neck share a potentially common pathogenesis with their counterparts in the retroperitoneum and mediastinum.[8] A periarterial location and encasement of vasculature or neurovascular bundles are seen in all three anatomic sites and point to a periarteritis as an underlying basis for the fibroinflammatory process. The only reported example of a tumefactive fibroinflammatory lesion outside of the head and neck (in the upper extremity) also had a neurovascular localization.[9]

A similar congeneric origin for the extracervical soft tissue sites of origin in the head and neck is difficult to invoke, especially for the paranasal sinuses. If the single photomicrograph in the report of Prichard et al[6] is representative, their cases (all paranasal sinuses) are misapplications of diagnosis.

The syndromic nature of some of the tumefactive fibroinflammatory lesions of the head and neck is manifested in a multifocal tissue involvement (eg, mediastinum, retroperitoneum). In fact, a supraclavicular presentation may be the first clinical evidence of a primary mediastinal process.

Radiographic appearances and gross operative findings can be misleading, and the fibroinflammatory lesions are often thought to be sarcomas before biopsy.

Histologic differential diagnosis is primarily related to fibromatosis, nodular fasciitis, and fibrosarcomas. We also add, for the lesions in the neck, the wall of a chronic abscess or chronic histoplasmosis. Recalling the histologic appearance of Riedel's thyroiditis and the idiopathic fibrosis of the mediastinum and retroperitoneum should place the surgical pathologist on the track of the correct diagnosis. In the mature form, the tumefactive fibroinflammatory lesion is a peripherally infiltrative fibrosclerosing lesion with collagenized or hyalinized stroma (see Figure). The vascular pattern is often inconspicuous except at the periphery and is unlike that of the fibromatoses or nodular fasciitis. The lesional tissue

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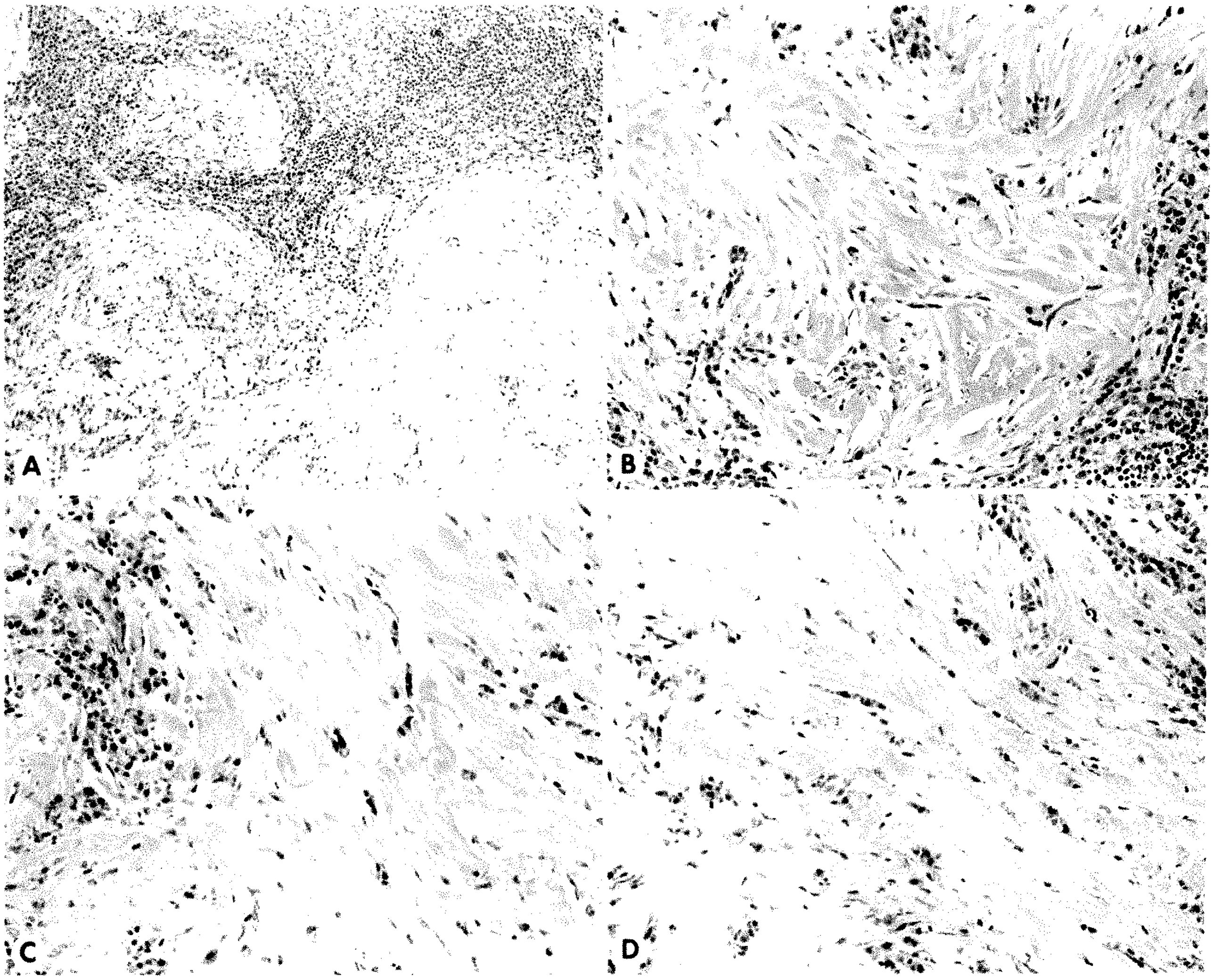

Tumefactive fibroinflammatory lesion of neck in 42-year-old man. A) Peripheral part of lesion showing fibrosclerosis bordered by chronic inflammatory infiltrate (H & E, original x40). B-D) Infiltrative, more central part of lesion, with typical hyalosclerosis and paucity of other cellular constituents (H & E, original x200).

is parvicellular, except for chronic inflammatory cells that can vary in density and number. Mitoses are absent to rare.

Despite the nonmalignant nature of the tumefactive fibroinflammatory lesions, local and regional recurrences are common, regardless of the form of the treatment. The latter has consisted of surgery, irradiation, high-dose corticosteroids, or a combination of these modalities — an indication that there is no optimum form. It is, however, suggested that corticosteroids be the initial treatment of choice.[4,5,9]

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To the Editor:

In their paper "Fine-Needle Aspiration of Salivary Glands: Its Utility and Tissue Effects" (*Ann Otol Rhinol Laryngol* 1992; 101:185-8) Dr Batsakis and colleagues mistakenly conclude that "FNA [fine-needle aspiration] cannot be supported as a systematic procedure in evaluating salivary gland lesions." Since our own extensive personal experience with the technique has led us to the opposite conclusion,[1] we feel it necessary to critically examine Dr Batsakis's arguments and at the same time explain why we believe that FNA should be systematically employed in the investigation of all salivary gland lesions, including neoplasms.

It is worth noting that although Dr Batsakis and his coauthors object to the use of FNA for the diagnosis of primary salivary gland neoplasms, they do acknowledge that the clinical utility of FNA of salivary glands is "unquestioned" for a long list of entities, including granulomatous disease, obstructive sialadenitis, lymphoepithelial lesions, lymphoepithelial cysts, lymphoma, and recurrent or metastatic carcinoma. While in many cases clinical findings may suggest one of these diagnoses, patients with these lesions may present with a dominant parotid mass that is indistinguishable from pleomorphic adenoma or other primary parotid tumors.

This diagnostic dilemma is especially true for intraparotid lymph nodes and parotid lymphoma, two entities that cannot be diagnosed on clinical grounds. Dr Batsakis acknowledges these lesions are readily diagnosed by FNA. Patients with reactive intraparotid lymph nodes can be spared unnecessary surgery if the diagnosis is made by FNA. When lymphoma is diagnosed by FNA, the surgical objective is biopsy rather than definitive local resection, and the surgeon will know in advance that he or she should submit fresh tissue to the pathologist for processing according to the lymphoma protocol used at the particular institution.

One reason underlying Dr Batsakis's deprecation of the value of the preoperative FNA diagnosis is his assumption that clinical findings alone can be used to reliably distinguish between neoplastic and nonneoplastic disease. However, errors in clinical diagnosis may occur in as many as 50% of cases.[2] It is precisely when FNA provides a diagnosis not anticipated by the clinical findings that FNA can play a critical role in influencing patient management. Even if one's only objective were to use FNA for those lesions that Dr Batsakis acknowledges are properly within the province of FNA, one would be required to perform FNA on all patients with salivary gland nodules, including those with a clinical diagnosis of a parotid neoplasm, to receive the maximum benefit of employing the FNA technique.

When FNA is used in a liberal manner, one can expect approximately one third of patients to be spared subsequent surgery.[3] While an unrestricted policy toward salivary gland FNA may engender a slightly increased cost for the majority of patients for whom FNA merely confirms a correct clinical diagnosis, very significant clinical benefits of the procedure will accrue to the minority of patients for whom the FNA diagnosis results in an important change in therapeutic approach. The benefits that routine FNA of salivary gland lesions provides to patients in terms of decreased morbidity and financial savings are completely disregarded by Dr Batsakis and his colleagues.

A more fundamental objection to the systematic use of FNA as a routine part of the diagnostic workup for patients with suspected salivary gland neoplasms is based on the view that the sole determinant for the treatment of parotid neoplasms is the anatomic relationship of the tumor to the facial nerve, and that the benign or malignant nature of the neoplasm and its specific histologic (or cytologic) designation is clinically irrelevant. For Dr Batsakis, an accurate FNA diagnosis cannot possibly have any real clinical value, since the type of surgical operation is dictated by gross anatomic factors, rather than the specific pathologic diagnosis.

Dr Batsakis's major assumption, that the only factor determining the nature and extent of surgical intervention is the relationship of the tumor to the facial nerve, is a misleading and erroneous oversimplification.

For example, one of our patients, a woman in her early twenties, presented with a parotid mass. Fine-needle aspiration was performed and a diagnosis of pleomorphic adenoma was rendered. At operation, it was noted that the tumor closely impinged on the facial nerve. Given that the FNA diagnosis was benign, every effort was made to preserve the integrity of the facial nerve. Sacrificing the facial nerve to assure complete removal of this benign tumor was not considered appropriate treatment for this patient, since the resulting facial nerve paralysis would have represented a devastating and unacceptable outcome from both a functional and emotional perspective. The cytologic diagnosis was a major factor in determining the approach to treatment for this patient. If the FNA diagnosis for this patient had been adenoid cystic carcinoma, a decision to resect the tumor with the involved segment of facial nerve would have been made as soon as the anatomic relationship of the tumor to the facial nerve had been established at the beginning of the operative procedure.

This case illustrates, as in other branches of medicine, that therapeutic decision-making can be a complex process in which numerous variables must be taken into account in order to establish the optimal treatment plan. Certainly, the clinician is better informed and therefore better equipped to make the correct decisions regarding therapy if the preoperative pathologic diagnosis provided by FNA is made available to him. In short, there are indeed clinical circumstances in which the extent of salivary gland surgery is determined, at least in part, by the specific pathologic diagnosis.

In addition to discounting FNA's clinical role, the authors claim that FNA causes damage to tissue that results in difficulties in subsequent pathologic assessment.

Figure 1 of their paper, which outlines their view of the possible histopathologic effects of FNA, is misleading. First, the Figure implies that necrosis is always an outcome of FNA. This is not true. In the vast majority of cases, neither micronecrosis nor macronecrosis is noted after FNA. Furthermore, the manner in which the Figure is constructed suggests that there is an equal probability of the three possible outcomes described. In the overwhelming majority of cases, FNA does not cause histopathologic changes that interfere with pathologic diagnosis.

In Figs 2-4, the authors present photomicrographs from a total of eight cases in which it is claimed FNA caused histopathologic damage that made interpretation of the pathology more difficult. Considering that over a lifetime of practice in which thousands of salivary gland cases have been reviewed by the senior author, only a handful of cases could be collected in which changes, presumably induced by FNA, caused diagnostic difficulties suggests to us that this phenomenon is extremely rare. In our own experience of more than 800 salivary gland FNAs, we have not encountered cases in which FNA-induced changes made subsequent histopathologic evaluation more difficult. To present these rare complications as a common occurrence is a significant distortion of the hazards associated with FNA.

Moreover, infarction or necrosis of salivary gland tumors can occur spontaneously, and this naturally occurring phenomenon, rather than prior FNA, may account for some cases of tumor necrosis presented by Dr Batsakis and colleagues. A case of spontaneous infarction of a parotid gland pleomorphic adenoma has been published by Layfield et al.[4] In Indianapolis, we have also encountered a case of spontaneous necrosis of a pleomorphic adenoma in which the extensive necrosis was first detected by FNA. Spontaneous infarction of other salivary gland tumors, such as Warthin's tumors, has also been described.[5-8] Squamous metaplasia, which Dr Batsakis attributes to previous FNA, can occur spontaneously in both Warthin's tumors[9] and pleomorphic adenomas, and may or may not be associated with concomitant tumor necrosis. To attribute all instances of necrosis of benign salivary gland tumors to prior FNA is not justified.

In summary, we believe that for patients presenting with salivary gland lesions, FNA should be considered as the diagnostic technique of first choice. The method is useful not only when the clinical index of suspicion for neoplasia is low, but also in those circumstances in which a neoplastic process is considered highly likely. In some cases, a clinical diagnosis of probable neoplasm can be refuted by FNA findings, and unnecessary surgery can be prevented. The specific cytologic diagnosis may contribute significantly to the clinician's therapeutic decision-making process. Fine-needle aspiration also makes it possible for the clinician to engage in preoperative counseling of the patient based on the hard pathologic data provided by the cytologic diagnosis. Proper informed consent for further treatment is more easily obtained if a pathologic diagnosis has been rendered. Patients with benign tumors such as pleomorphic adenoma or Warthin's tumor can be immediately reassured by FNA findings that they have a benign rather than a malignant neoplasm, and this information is of inestimable value for patients who may be anxious regarding the nature and prognosis of their condition. The treatment of patients with malignancies diagnosed by FNA can be expedited. This may be especially important in those cases in which the original clinical diagnosis was benign. The fact that all of this very useful information can be supplied to the patient and physician within minutes of performing the aspiration is obviously of added benefit. While occasionally, FNA may induce alterations in the tissue that make subsequent histopathologic diagnosis somewhat more difficult, these changes occur very infrequently, and are a cause of diagnostic confusion in only the exceptional case.

For all of the reasons described above, we support the continued use of FNA for the routine investigation of all patients with salivary gland lesions. In our opinion, Dr Batsakis and his colleagues grossly underestimate the clinical value of FNA of the salivary gland and unfairly exaggerate the significance of rare histopathologic changes that on occasion may be induced by the technique. In part, their negative opinion regarding salivary gland FNA may reflect the isolation from clinical practice that affects many histopathologists. We anticipate that our clinical colleagues, who in general widely support the use of this diagnostic technique, will continue to do so on the basis of their own experience with FNA.

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To the Editor:

Drs Cramer, Layfield, and Lampe are clearly advocates of fine-needle aspiration (FNA). Their response to our paper covers the usual arguments: cost savings, avoiding unnecessary surgery, frequency of clinical diagnostic errors, planning of surgery, etc.

They mistakenly attribute our views on aspiration biopsy of the parotid gland and submandibular gland to an "isolation from clinical practice that affects many histopathologists" and imply *their* clinical colleagues widely support use of the technique.

Abstract isolation by surgical pathologists or cytopathologists is an unaccepted mode of practice and is especially condemned in dealing with lesions of the head and neck. The pathologist who does not fully understand this not only will lose his or her clinicians' confidence, but may lose his or her job.

As for wide support of FNA biopsy of salivary gland lesions, the reservations expressed by Spiro[1] (Memorial Sloan Kettering Cancer Center) and Smith and Fleming[2] (Royal Melbourne and Peter MacCallum Hospitals, Australia) are just two contradictions. Spiro[1] asks the main question we raised, and that is whether the procedure facilitates treatment. He goes further in indicating it is unnecessary most of the time, but is helpful when there is a suspicion of an inflammatory or neoplastic process in parotid lymph nodes, or when the *size* and *location* of the parotid mass suggest that a "particularly tedious facial nerve dissection can be anticipated."

Spiro's[1] reference to facial nerve dissection is fully in concert with our point that FNA does not give any indication of the tumor's relation to that vital structure. The extent of any parotid gland surgery is primarily determined by the size of the tumor and the presence or absence of local extension — not the histology of the tumor. Spiro's[1] axiom that the facial nerve should be preserved unless it is adherent to or involved by the tumor nearly negates the clinical utility of an FNA. Extended parotid gland surgery and radical neck dissection are also not dictated by cytopathologic diagnosis. Indeed, given the poor survival in patients with extensive, high-grade neoplasms, radical extirpation is a surgical, not cytopathologic, decision. It is also telling that lymph node metastases occur in about 25% of patients with carcinomas of the parotid gland, and most of these are clinically evident at the time of admission.

As for lymphomas limited to the parotid gland, it is of interest that in a Cleveland Clinic series, there was no statistically different outcome found between biopsy and parotidectomy for diagnosis.[3]

Our Fig 1 had a legend stating it outlined three *possible* histopathologic effects of FNA. Cramer et al are correct in saying the majority of aspirations don't show these, but they miss the point of the diagram. As for the frequency of the three effects, it cannot be assessed with any accuracy. Over a 3-year period we have seen 29 examples, all sent for consultation after aspiration biopsy because of some degree of obscuration of histopathologic detail and, in nearly every instance, an equivocal cytopathologic diagnosis or unsatisfactory aspirate.

We miss the point the authors try to make on spontaneous infarct of pleomorphic adenomas. It is rare. One of the authors, Dr Layfield, has even reported what he considers to be the first reported case.[4] Odds are that an infarct of a pleomorphic adenoma found after FNA is attributable to that procedure, and not to a spontaneous event.

The operative words in our paper were *systematic procedure* and *clinical utility*. They are not mutually inclusive. Dr Cramer and his co-workers have not convinced me of the usefulness of routine, systematic employment of FNAs for parotid tumors.

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To the Editor:

I read with interest the Imaging Case Study of the Month (Penetrating Trauma of the Jugular Foramen, *Ann Otol Rhinol Laryngol* 1992;101:452-4) by Overholt et al, in which the role of computed tomography evaluating the path of a wooden foreign body is well demonstrated.

Of note, however, is the incorrect assumption that the appearance of a wooden foreign body as a gas-density structure would imply an old, dried-out stick, whereas a live piece of green wood would be closer to soft tissue or water density.

I would think the correct explanation is the partial volume artifact, well known to most experienced computed tomogram operators. I would suggest that partial voluming of air retained along the foreign body track accounted for the gas-density measurement. Had the wooden splinter been scanned alone after extraction, it would have measured well above soft tissue density. A recently published case we have seen illustrates this principle clearly,[1] in which a retained wooden splinter measured gas density because of retained gas along the track of the foreign body. The partial volume principle states that the value of Hounsfield units assigned to a particular area is a mean value for the tissue contained in the volume of the area. If the area contains structures of various densities, each structure contributes proportionally to the Hounsfield unit reading. Very-low-density objects (such as air along the foreign body track) contribute corresponding density values that when averaged with the rest of the structures in the volume result in abnormally low Hounsfield unit readings being assigned to the entire area.[2]

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To the Editor:

We were most interested to read Dr Woo's paper (Acquired Laryngomalacia: Epiglottis Prolapse as a Cause of Airway Obstruction, *Ann Otol Rhinol Laryngol* 1992;101:314-20).

We have recently had a case of what we believe is acquired neonatal laryngomalacia. The male infant was born at 41 weeks' gestation following a Kielland's forceps delivery. This was a difficult procedure, requiring rotation of the infant, and followed two attempted ventouse extractions. At birth he had a respiratory rate of 60 per minute and was initially cyanotic and irritable, but had no stridor or intercostal recession. His Apgar scores were 8 at 1 minute and 9 at 5 minutes. No trauma to the neck was visible. A chest radiograph demonstrated clear lung fields. Lumbar puncture revealed 80,000 red blood cells per cubic millimeter of cerebrospinal fluid (CSF) and a xanthochromic supernatant, consistent with subarachnoid blood. At 17 hours of age the infant had become more irritable and tachypneic. Inspiratory stridor had developed, with a tracheal tug and intercostal recession.

Microlaryngoscopy under general anesthesia was performed. The epiglottis was of normal shape, the aryepiglottic folds were of normal length, and the arytenoids were not bulky. Thus, the classic features of congenital laryngomalacia as described by McSwiney et al[1] were absent. The glottis and subglottis were also normal. However, as spontaneous respiration returned, the epiglottis was seen to furl and become drawn into the laryngeal inlet, producing stridor.

Over the subsequent 8 days the stridor diminished and the infant became less irritable. At 11 days no audible stridor was present, and he had no intercostal recession at rest.

We suggest that in this case traumatic delivery resulted in central nervous system injury, as supported by the finding of blood in the CSF. Subsequent impairment of pharyngeal and laryngeal neuromotor control, as suggested by Woo in adult cases of central nervous system injury, may also then have been responsible for the acquired laryngomalacia in this neonate.

Stridor due to congenital laryngomalacia is characteristically present at birth, increases in severity during the first year of life, and thereafter begins to resolve spontaneously.[2,3] The latency of onset, early resolution, and absence of any classic anatomic features support an acquired causation for this observed case of laryngomalacia in a neonate.

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To the Editor:

The report by Benton et al (Plasma Cell Granuloma of the Middle Ear and Mastoid. Case Report, *Ann Otol Rhinol Laryngol* 1992;101:92-4) on the "first" case of plasma cell granuloma (PCG) of the middle ear and mastoid raises important questions regarding both the diagnostic workup and the treatment of their patient.

A poorly characterized benign disorder, PCG most commonly involves the lung, gastrointestinal tract, and salivary glands.[1] In view of the nonspecific nature of the histologic findings, it is a diagnosis to be made only after careful exclusion of other benign and malignant conditions. Even more caution should be exercised when the lesion occurs in an atypical site, as in this case.

Benton et al do not indicate if investigations to exclude an infectious cause were performed. Histology alone cannot exclude infections in the sinuses,[2] and the reliance on a limited workup to exclude infections in this region can prove disastrously wrong.[3] Low-grade forms of Wegener's granulomatosis have been described in which paranasal sinus and middle ear involvement was present for periods of up to 18 years before a diagnosis was made.[4] No mention is made if this possibility was considered in this patient.

As complete resection of the patient's tumor mass was achieved and a 10-year disease-free interval had followed the initial procedure, the decision of Benton et al to proceed to radiotherapy is questionable. The prognosis in cases of PCG treated by surgery alone is good,[1] and radiotherapy to the middle ear region of this young patient carried the risk of cerebrovascular accidents, malignancy, and radionecrosis of neural tissue.

A recent report purporting to describe the "first" case of PCG of the nasal cavity illustrates the need for caution in making this diagnosis.[5] The histologic appearance in this case was similar to that described by Benton et al, the plasma cells present were polyclonal, and tests for acid-fast bacteria and fungi proved negative. The patient was treated with both surgery and radiotherapy. A later review of the original histology revealed positive staining for *Klebsiella rhinoscleromatis*, and this was confirmed at the time of disease recurrence, 2 years after treatment.[3]

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BOOK REVIEWS

The Esophagus

Donald O. Castell, editor. Hard cover, illustrated, indexed, 842 pages, 1991. Little, Brown; Boston, Mass, $150.

Dr Castell has put together a most authoritative and comprehensive text that will surely serve as the standard for students and professionals interested in the workings of the esophagus. To produce this work on esophagology, he has added the experience of experts on the esophagus from around the world to his own experiences over a period of 20 years. All aspects of medicine and surgery as they relate to the esophagus are given attention in the text. One might wonder at the size of the book (825 pages, 3.75 pounds), since it is devoted to the simplest of organs — a hollow, muscular tube with a sphincter at each end. Consider, however, that an estimated 10% of our population report experiencing "heartburn" every day and one third of the population has intermittently suffered other esophageal symptoms.

Although the 40 chapters are not organized in any obvious sequence, each is generally concise and contains little repetition of information — not an easy feat for a multiauthor text. The print is easy to read, the book is generally up-to-date, and many recent bibliographies are included.

Clear explanations of disease mechanisms affecting the esophagus are presented by a number of the authors. The first chapter devotes much attention to the anatomy of the esophagus, creating an environment for the understanding of the disease processes that affect it. Another chapter addresses disorders that cause oropharyngeal dysphagia, differentiating this from esophageal dysphagia. Esophageal abnormalities in systemic disease are discussed in another chapter. The features of progressive systemic sclerosis (scleroderma) show that the clinical manifestations of esophageal involvement can vary widely. The microflora and the immune aspects of the esophagus are equally well treated in Esophagitis in the Immunocompromised Host. Several discussions of gastroesophageal reflux, endoscopy, and biopsies make clear the state of the art as it is available to the clinician. In addition to other conditions, caustic injuries of the esophagus, viral and bacterial infections, Mallory-Weiss tear, and cancer are all covered, from their cause to the medical and surgical treatment.

The editor did not neglect any aspect of esophageal disease in preparing this book. Its scope crosses several scientific disciplines and integrates knowledge for the otolaryngologist–head and neck surgeon as well as the gastroenterologist. It would well serve the reference libraries of primary-care physicians and surgeons.

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Otolaryngology–Head and Neck Surgery

William L. Meyerhoff and Dale H. Rice, editors. Hard cover, illustrated, indexed, 1,168 pages, 1992. WB Saunders, Philadelphia, Pa, $160.

The goal of the editors of this tome was to provide more comprehensive coverage of otolaryngology–head and neck surgery than has ever been presented in any single volume, while making the information more available than that offered in multivolume works. To achieve this, they asked 83 specialists to cover a wide array of medical topics and surgical procedures. The resulting 60 chapters, from which reviews and references have been excluded, are divided into seven parts: General Considerations; Ear; Nose, Paranasal Sinuses, and Nasopharynx; Oral Cavity, Oropharynx, Hypopharynx, and Salivary Glands; Larynx and Neck; Disorders of Soft Tissue and Skeleton; and Related Topics. Each chapter, however, is limited to the philosophy and approach of the author(s) covering it.

As early as the first chapter, which is divided into two sections, the reader becomes aware that this book offers some unusual features. Although perhaps not the best cosmetic example, a picture of an operated ear accompanies the discussion of postoperative care of a radical cavity in chapter 1B. Within this same part (part 1) there appears an even more unusual occurrence for a book on otolaryngology–head and neck surgery: chapter 4, Speech Pathology: Evaluation and Treatment of Speech, Language, Cognitive, and Swallowing Disorders. The nonmedical author (PhD) presents a very informative and logical outline for the physician to use in diagnosing and managing these disorders. Unfortunately, his bias for sign language as the communication method of choice for the hearing-impaired is at the expense of other forms of communication, such as auditory-verbal. There is also little insight shed on attention deficit disorders and dyslexia in this chapter. Nevertheless, the mere fact that a chapter is devoted to speech and language problems makes this book unique, and confirms the editors' desire to present comprehensive coverage.

A number of possible causes for sudden, fluctuating, or gradual sensorineural hearing loss and therapeutic measures for each of them are examined in one chapter. The accuracy of some of the statistics related to improved hearing following endolymphatic sac decompression or vestibular nerve section in Meniere's disease is questionable, although the author does follow them with literature citations. The various approaches to vestibular nerve section are more adequately reviewed in the chapter on vertigo. The authors of that chapter do not distinguish the symptoms and test results seen in central vertigo from those seen in peripheral vertigo, however.

Noninflammatory lesions of the ear and skull base are well covered, with useful information for the physician clearly given. In a particularly well-done discussion of acoustic neuromas, insight is given into the developments that have reduced the surgical risks over the last 40 years or so. Stressing the need for an impeccable history and thorough neurologic examination in evaluating patients for these lesions, the author considers the similarities and differences between their symptoms and those seen in other conditions, and the use of various diagnostic modalities. Addressing cholesterol granulomas, the author points out that these are adequately treated by permanent drainage, and presents the criteria, advantages, and disadvantages of several surgical approaches.

The chapter on inflammatory and granulomatous diseases of the nose and paranasal sinuses is quite brief. It is difficult to understand why these authors chose to include many conditions not frequently seen in this country, but not endoscopic nasal sinus surgery, a subject in need of more exploration and explanation.

The editors have quite successfully assimilated very useful clinical information, including overviews of subjects not usually found in other texts. The usefulness of this book is not limited to specialists in otolaryngology–head and neck surgery. It deserves a place in the library of every physician who might encounter patients with complaints in the head and neck.

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Transplants and Implants in Otology — II

N. Yanagihara and J.-I. Suzuki, editors. Hard cover, illustrated, author index, 413 pages, 1992. Kugler Publications, New York, NY, $125.

Increased interest and escalated use of transplants and implants in otology most likely precipitated the first (1987) and second (1991) International Symposia on Transplants and Implants in Otology. This volume contains what the editors have deemed to be the most significant contributions of the second symposium. Beginning with a statement on ethical issues in otology, they proceed to present discussions of the use of allograft and xenograft in middle ear surgery, plastic, metallic and ceramic implants, rehabilitation of radical cavities, biomaterials and adhesives in ear surgery, basic and clinical aspects in ear surgery, bone-anchored implants, cochlear implants, and implantable hearing devices.

It is noted that ossiculoplasty has been greatly enhanced by the use of biomaterials, particularly ceramics. However, a caution is given to surgeons to observe a few essential rules, specifically the need for working on a noninfected operative field. The author of this paper prudently recognizes that it takes not only a technically skilled surgeon, but one who is also an astute physician to assess all factors so that his or her efforts will not be sabotaged. These factors include the condition of the immune defenses, the quality of the reactions of the upper airways, and the status of the eustachian tube and tissues of the middle ear. It is also pointed out that the use of biomaterials in replacing the external auditory meatus is problematic and that their use in reconstructing the tympanic membrane remains in the experimental stages.

The use of homografts, especially en bloc homografts, has not lived up to expectations in restoration of the conductive system of the middle ear, even though good functional results (conversational hearing) may be achieved. That appears to be the opinion of the author on that subject, who was one of the pioneers in the area. In his opinion there will always be at least a 5- to 10-dB difference between bone and air conduction. He has also found total restoration of the tympanic cavity with a good mucosal covering to be very difficult, and the restoration of a functional ossicular chain even more difficult in a middle ear that has been completely destroyed by an inflammatory process. Even so, he maintains that the procedure he describes has proven to be the most suitable one for reconstruction of the conductive system, and explains why in this chapter.

Rather than enlightening the reader on how to improve the outcome of ossicular reconstruction, the chapter on that topic appears to present all the statistics one would want on ossicular reconstruction. When results are discussed, an important question is not answered: Does the patient agree with the surgeon's appraisal of the final outcome?

Several good points are brought out in the comparative study of incus replacement prostheses using a temporal bone model. 1) The best contact point of the tympanic membrane for the reconstruction of the missing incus appears to be the posterior half of the tympanic membrane. 2) The amount of tension, as well as the angle, of the prosthesis between the tympanic membrane and stapes head is important in providing optimal results. 3) The Ceravital prosthesis performed better than the Plastipore because of its weight and stiffness. 4) The tensor tympani muscle has a negligible effect on sound transmission after introduction of an incus replacement prosthesis, as long as the prosthesis is not excessively long.

One hundred pages of this book are devoted to cochlear implants. They are informative and give practical conclusions. Of particular note is the discussion on implant length, insertion, and utilization of a number of electrodes. It seems to this reviewer, however, that cochlear implants are the most-researched device of all body implants today, and that papers and articles on them outnumber the actual recipients of the device.

The clinician involved primarily in chronic ear work will find the book quite useful, for the editors have prepared an excellent review of that subject.

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